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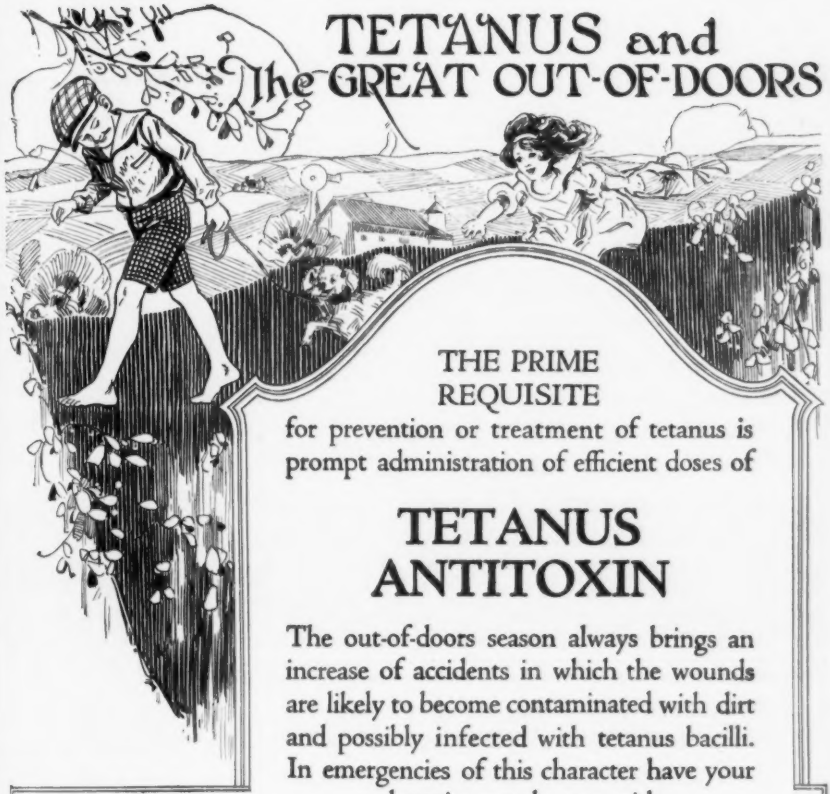

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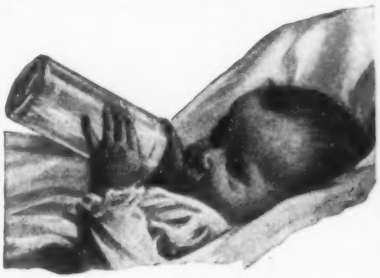

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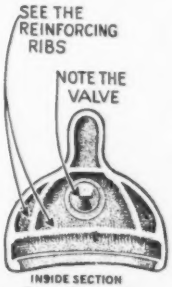

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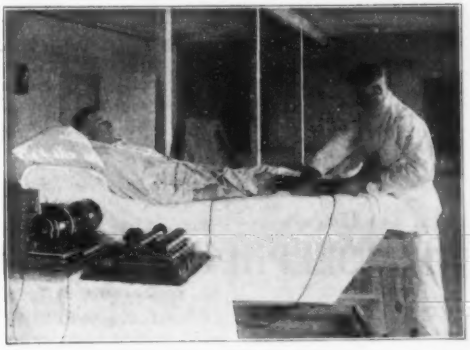

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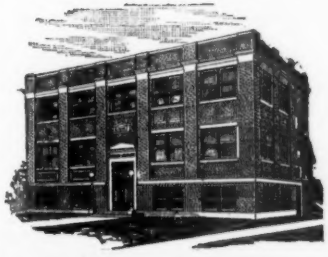

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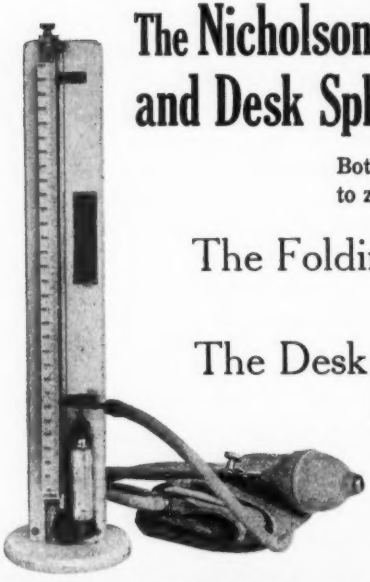

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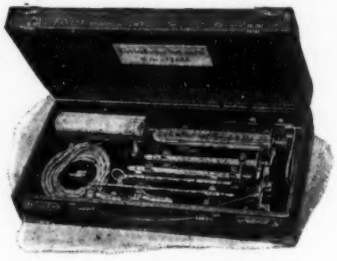

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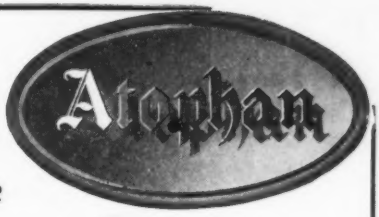

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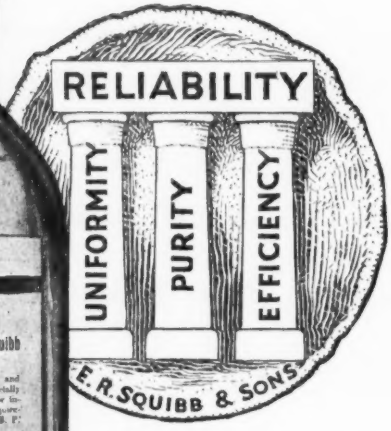

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THE

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OF THE MEDICAL SCIENCES

JUNE, 1920

ORIGINAL ARTICLES.

CAUSES AND DEFINITION OF CANCER.

By Leo Loeb, M.D.,

ST. LOUIS, MO.

(From the Department of Comparative Pathology, Washington University Medical School of Medicine, St. Louis, Mo.)

In the present article we wish to summarize as briefly as possible our knowledge of the causes of cancer as far as our information in this field permits us to do so at present without exceeding the range of probabilities. The following factors may enter as causes of cancer:

(*a*) External stimulation of a mechanical or chemical nature.

(*b*) Internal chemical stimulation, especially through the action of internal secretion.

(*c*) Heredity, which includes various not yet well-defined factors, some of them probably identical with the other "causes."

(*d*) Embryonal character of tissue or disturbances of embryonal development; this includes parthenogenetic development of the ovum.

(*e*) In an indirect way age may enter as a factor.

(*f*) Contact between normal and cancerous tissue.

(*g*) A possible effect of microörganisms.

(*a*) *External Stimulation.* Observation of cancer in man has abundantly proved the significance of long-continued irritation or in some cases apparently even of a single trauma in the origin of

cancer. The same factor may play a part in cancer of animals. We have, for instance, shown that in this country the favorite seat of cancer in cattle is the inner canthus of the eye, where foreign bodies are liable to lodge and to cause irritation.

A number of investigators have attempted in a similar manner to produce cancer experimentally. The earlier experiments did not succeed, probably because the irritation was not applied over a sufficiently long period of time. (Hanau, Brosch.)

More recently similar attempts have been successful (Pierre Marie, Raulot-Lapointe and Clunet, Fibiger, Yamagiwa and Ichikawa). Through the application of roentgen rays two sarcomata have been produced at the root of the tail of rats, and carcinomata, some of which were metastasizing and transplantable, have been produced in the stomach and tongue of rats and in the stomach of mice after feeding with nematodes which settled in the stratified epithelium and stimulated it. Through the feeding of mechanically irritating material a cancer of the tongue has been produced in a rat. Following the application of tar carcinomata developed in the skin of the ear of rabbits. While those experiments are essentially a confirmation of what observation has shown to take place in nature, they are of the greatest significance, not because they establish a hitherto unknown cause of cancer but because they open up a new field for the experimental analysis of the conditions under which this cause acts and because they offer a chance for its quantitative analysis.

In a tentative way we may draw certain conclusions on the basis of these investigations.

1. There seems to exist a graded series of transitions from the normal growth energy and cell motility to the increased growth energy and motility of cancer. On the whole, the first stages seem to be similar in different kinds of cancers (similarity in the first stages of the experimental cancer of stomach, tongue, skin).

2. The increase in growth energy and mobility and in the length of time over which this increase persists after the stimulus has ceased to act appears to be gradual. Various intermediate stages seem to exist.

3. It is probable that in the experimental cancers produced by Yamagiwa and Ichikawa, and perhaps even in those of Fibiger the last stage, which we find in many spontaneous cancers of the rat and mouse and of man, had not yet been reached. Thus the experimental cancers in the ear of rabbits retrogress in a much greater proportion of cases than do spontaneous cancers. The most virulent case of cancer in the stomach of mice died out after a few transplantations.

Transplantability as such is not necessarily a characteristic of cancerous tissue. Many spontaneous cancers cannot be transplanted successfully. And, on the other hand, we did accomplish

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a serial transplantation of a benign tumor in a rat. It likewise died out after a few transplantations. Even normal tissue can be transplanted repeatedly. But each kind of tissue maintains, on the whole, the growth energy characteristic of it, and this is one of the essential distinguishing features between cancer, benign tumor and normal tissue. Besides cancer tissue, proliferating very actively, may escape the action of homoiotoxins much more effectively than normal tissue. Whether the early dying out of Fibiger's tumor was due to accident or to a gradual weakening of the growth energy or to a combination of both these factors, cannot be stated by us with certainty. It is probable that in this case the increase in growth energy had persisted over a considerable period following cessation of the stimulus; but that the increase had not yet become permanent.

This conclusion seems to apply with much greater definiteness in the case of the experimental cancers in the rabbit ear. The tissues used in these experiments are evidently relatively resistant to the cancerous transformation, as evidenced by the fact that spontaneous cancers have not been observed in the ear of the rabbit and are very rare in the stomach of rats or mice.

4. While it is thus very probable that the transition from normal to cancerous tissues represents a series of stages, the transition from one stage to another may be abrupt. The cancerous tissue may differ sharply from the precancerous tissue morphologically and biologically. It is, however, possible that a continuous not visible change precedes this abrupt transition. It is probable that also in man certain cancers have not yet reached the last stage of cancerous transformation. In certain cases their actual and potential proliferating power seems to be as yet relatively low and it is not improbable that in some cases these changes have not yet become permanent. At present the demarcation between those transitional stages which are and which are not yet cancerous is to some extent arbitrary.

5. We may furthermore conclude that the earlier the stages in the transformation leading to cancer the greater is the tendency to retrogression in the cancerous transformation which can be produced experimentally, and that the earlier stages yield more readily to the action of agencies which tend to destroy them.

(*b*) *Internal Secretion.* Three sets of experiments might be cited as disproving the significance of internal secretion as one of the causes of cancer: (1) The lack of success in the attempt of surgeons to cure cancer of the mammary gland through castration. (2) The fact that in castrated cattle and horses cancer is, on the whole, as frequent as in not-castrated animals. (3) The fact that in castrated mice inoculated tumors grow in a manner not very different from that observed in normal control mice. Yet none of these facts disprove the significance of internal secretion in the development of cancer. The first observation is in all probability to be attributed to the fact that internal secretion has no definite influence on the

growth of cancers after they have once developed. The negative result in the second observation is due to the fact that the relation between internal secretion and the development of cancer is not a general but a specific one. Castration cannot influence the origin of cancers in organs in which the growth processes are not normally directly dependent upon the internal secretion of the ovary. The third observation which relates to the condition under which inoculated tumors, "homoiotumors," cancers which are already well established, grow, can have no bearing on the problem of the origin of tumors. In two series of experiments we could indeed show quite definitely that castration has a definite influence on the origin of mammary cancer, which is the usual cancer in mice. Not only can it be proved that a hormone given off by the ovary regulates those tissue changes which lead to the development of cancer of the breast in mice, but it can, furthermore, be shown that the influence of this hormone is a quantitatively graded one. If the quantity of this hormone, which had a chance to act on the tissues, exceeds a certain limit, cancer appears as frequently as in non-castrated controls (castration at the age of eight to ten and one-half months); if an intermediate quantity of the hormone has been active the cancer rate is noticeably diminished and the cancer seems to appear later in life (castration at the age of five to seven months); if the quantity of the hormone is still further restricted cancer does not appear at all or only exceptionally (castration at the age of three to five months). After an intermediate and late castration tumors may not only appear in the first-age period, but even tumors which in control mice appear as late as the third-age period are not prevented from developing. This suggests the conclusion that the first tissue changes which eventuate in the development of cancer occur at a much earlier period in life than might have been expected, and that castration affects these primary tissue changes rather than the secondary transformation of these changes into fully developed cancer.

Experimental investigations have made possible in this case a quantitative analysis of a definite cause of cancer, and it will now probably be possible to analyze experimentally in an exact manner the conditions underlying the origin of cancer of the breast in mice. The effect of hormones on the development of cancer is a specific one; a hormone influences the development of cancer only in those organs to which under normal conditions it has a specific relation. We may assume that relations similar to that between cancer of the breast and the ovary exist also between the development of other kinds of cancer and the organs with which they are related through internal secretion. It follows from our experiments that attempts to cure cancer of the breast after it has once been established cannot be successful. Our experiments have established, furthermore, the fact that nursing and the injuries due to it or pregnancy

in general have only a negligible influence on the frequency with which mammary cancer develops in mice.

(*c*) *Heredity.* It is commonly assumed that heredity plays no part in the origin of cancer in man, and as late as 1910 Bashford expressed the opinion that heredity has no significance in the etiology of cancer in general. The prevalence of this view is due to the fact that the methods used were those usually applied in human mortality statistics; the frequency with which cases of cancer occur in the ancestry of persons dying from cancer and other diseases was compared. No noteworthy differences could thus be found in man at least among the white races. Tyzzer and Murray approached the same problem in the case of mice with somewhat similar methods. Murray compared the frequency of cancer in these animals among those individuals whose mother or grandmother had cancer, on the one hand, and among those in whom cancer had not been observed in the direct ancestry but may have occurred in the great grandparents. Murray found on the average about 20 per cent. of cancerous mice among those whose direct ancestors had suffered from cancer and 11 per cent. among those whose direct ancestry had been free from cancer. In certain age classes the cancer rate of both kinds of mice showed only a very slight difference, and in one age class the cancer rate was even higher in those whose direct ancestry had not been affected by cancer. Nevertheless the figures of Murray point to the conclusion that heredity plays a part in cancer of mice. There are, however, certain difficulties implied in the method used by this author. A certain mouse may be cancerous and still the hereditary tendency in the family of such a mouse may be much less strong than in another mouse which did not die from cancer. This method can therefore at best only make probable the existence of a hereditary factor in the origin of cancer in mice. It cannot give definite knowledge of the significance of heredity, and in particular it cannot give an insight into the quantitative factors which are concerned in heredity. In order to determine to what extent the hereditary tendency to cancer varies in different families, whether the hereditary tendency to cancer in a certain strain is a constant or may become modified under certain conditions, and what the laws of heredity are in hybrids between strains rich and poor in tumors, we have to use a different method and try to follow the fate of separate families or strains of families through successive generations. Earlier observations on the so-called endemic occurrence of cancer in cattle and rats suggested to us the possibility that heredity might be responsible for this condition. But it was only about twelve or thirteen years ago that we began with Miss Lathrop to make observations on the difference in hereditary predisposition to cancer in the different strains of mice which were raised in her breeding establishment. Preliminary observations indicated differences in the cancer rate in different

strains. Since 1910 we have kept systematic records of the cancer incidence in the various strains on the cancer age and on the effect of hybridization on the cancer rate in the offspring.

In thus keeping families or strains of mice separate through successive generations we find that the cancer rate in different strains shows extreme differences. While in some families it may be as high as 70 to 80 per cent. or even higher, in others cancer may be very rare or absent. All intermediate degrees are found in other families. In some cases we could separate substrains differing sometimes but not always in color and other characteristics and which had a cancer rate different from that of the main strain. In this case we had in the beginning probably to deal with mixed material from which a more homogeneous line could be detached. In those strains in which the cancer rate is high an absolutely greater number of tumors appear usually in young animals than in those with a low tumor rate; but a certain difference exists in this respect in certain strains and within certain limits the cancer age seems to be a hereditary characteristic at least in the case of some families. Thus a number of strains may have a similar cancer rate, but in some of them many cancers appear in relatively young animals, while in other strains the great majority of cancers appear in older mice.

If we follow such strains through a considerable number of successive generations we find in many of them a surprising constancy in the cancer incidence. In some cases, however, changes occur which can in all probability be referred to one of these two conditions: (1) A selective action takes place as the result of which certain substrains with a somewhat different hereditary tendency to cancer become predominant in number, usually as the result of a more or less accidental condition, or (2) as the result of long-continued inbreeding not accompanied by selection of the strongest individuals the character of the strain changes in certain respects, and these changes entail corresponding changes in the cancer rate. A lowered vitality and breeding activity were accompanied by a lowering in the cancer rate.

If we hybridize different strains or substrains the cancer rate of the offspring is as follows: (1) In cases in which the cancer rate and cancer age of both parent strains are similar the cancer rate and age of the hybrids correspond to that of the parents. (2) If the cancer rate and age of the two parents differ very much the cancer rate of the offspring is often intermediate; there occur, however, all transitions from an intermediate condition to various degrees of dominance of one of the parents over the other. The parent with the higher tumor rate was, however, dominant in a considerably larger number of cases than the parent with the lower tumor rate in the strains with which we carried out our experiments. There is an indication that possibly in certain cases the mother

strain is of more importance in determining the cancer rate of the hybrid than the father strain, and that therefore one or more of the hereditary factors determining the development of cancer may be sex-linked. At present this is merely a suggestion, and further investigations must decide definitely whether or not such a relation exists.

From all these experiments we may, as we have pointed out previously, draw the conclusion that the hereditary tendency to cancer does not follow the laws of simple Mendelian inheritance of monohybrid characters; that it can, however, be explained according to Mendelian principles if we assume the presence of multiple hereditary factors. The inheritable tendency to cancer apparently does not consist in a tendency of the animal to develop cancer indiscriminately in any part of the body, but only in particular organs. Thus according to our observations mice with a very high incidence of mammary cancer do not usually develop cancer in any other organ but the breast. Miss Slye's discovery of families of mice with an inheritable tendency toward cancer in organs in which usually cancer occurs not at all or only very rarely is in agreement with this conclusion.

While it is now generally conceded that in the cancer of mice hereditary factors are of significance, it is, on the other hand, almost universally accepted that in human cancer hereditary factors do not play a part and that therefore a marked difference exists in this respect between these two kinds of cancer. However, it seems to us that a critical review of the evidence at hand does not justify such a conclusion; on the contrary, there is much evidence for the view that conditions are similar in both cases The apparent difference is probably due to two factors: (1) In man the usual statistical methods are employed. Thus it is determined whether in the ancestry of persons affected by cancer the cancer incidence is considerably greater than in persons not thus affected. We have seen that even in the case of mice such statistical methods can at best give only a very inadequate view of the great differences caused by heredity in the cancer rate of different strains. (2) If we assume that in mice a constant interbreeding between diverse strains differing markedly in their cancer rate had taken place, there would undoubtedly after a certain period of time have occurred an equalization in the cancer rate of the various mixed families. Through statistical methods no or at best only a slight difference would have been detected in the ancestral cancer rate of individuals affected by cancer and those not thus affected. An occasional more noticeable difference encountered would probably have been explained as a chance occurrence. Yet while the interbreeding would to some extent have equalized the cancer rate in different families, it would therefore not have destroyed the hereditary factor of predisposition, but it would merely have distributed it quanti-

tatively in such a way that no marked differences could have been discovered between different families. Now this is what actually has taken place among the civilized races. Divergencies in the hereditary cancer rate which originally would perhaps have been quite noticeable might have been obscured through constant intermarriages. There is some evidence which seems to sustain such a conclusion. If we compare the cancer rate in human strains in which such intermarriages have not taken place, we find indications of a difference in the cancer incidence in these strains. Thus there can be little doubt that the aborigines in Africa and elsewhere differ in many cases markedly from the majority of the civilized people in their incidence of cancer and in the kinds of cancer from which they suffer. The negro in Africa and the pure Indian in this country may be cited as examples. Even among civilized people divergencies in the cancer rate seem to develop if the population is of a more sessile character and if distinct strains are formed through constant inbreeding and lack of intermarriages between different strains. At least this seems to hold good in certain parts of Norway according to the observations of Garmann. In America the cancer rate of the negro seems to be lower than that of the white race but higher than that of negro in Africa; this may be due to frequent intermarriages which have occurred between the two races. It is, however, possible that changes in the mode of living may also play some part in this result.

It is furthermore a well-established fact that various conditions which predispose to cancer are hereditary, such as pigmented nevi; the same holds good in the case of other hereditary abnormalities. Taking into consideration all these facts we may consider it probable that heredity is also a factor in the origin of human cancer, but that in the latter interbreeding and perhaps other factors have obscured this significance of heredity.

Such an interpretation may perhaps be of service in explaining, at least in part, the increase in the cancer rate which has been observed in all countries where statistical methods are employed. While it is still possible that this increase is only apparent, yet there is some evidence which makes at least probable the conclusion that an increase has actually occurred in most civilized countries. Now, if we assume that in human cancer the same conditions prevail which we found in cancer of mice, where in the case of our strains the higher cancer rate of one parent dominated over the lower cancer rate of the other in the majority of cases, such a slow increase in the cancer rate might be foreseen as the result of constant intermarriage. If intermarriage between individuals differing slightly in their hereditary tendency to cancer occurred constantly, it might lead to a gradual slow increase in the cancer rate, which would continue until at last the hereditary tendency has been almost equalized through constant interbreeding. Other conditions

such as changes in the mode of living which are taking place almost universally may perhaps be a contributing factor.

As to the character of the factors underlying the hereditary tendency to cancer our knowledge is not yet definite. We may, however, assume that in all probability different factors play a part. In some cases it depends apparently on differences in the readiness with which the transition from the earlier to the later stages of cancerous transformation are made by various tissues of the same individual and the same species. Differences in the amount of resistance which analogous tissues offer to acceleration in growth may be found normally. Thus we have observed that the mammary gland of the guinea-pig opposes a greater resistance to proliferative stimuli emanating from the ovary than the mammary gland of the rat or rabbit. On the other hand the epidermis of the guinea-pig possesses inherently a greater proliferative activity than the epidermis of the rat or pigeon. A quantitatively graded reduction in the amount of ovarian internal secretion still permits the development of mammary cancer in certain individuals but not in others.

In Fibiger's as well as in Yamagiwa's and Ichikawa's experiments the tendency of the tissues to take the first steps toward an increase in proliferative activity was widespread; in the later stages the tendency to acceleration in proliferative activity diminished and became restricted to a smaller number of individuals which were perhaps endowed with a greater lability of the tissues. In other cases the hereditary tendency consists in the hereditary transmission of cell groups which are especially liable to assume greater growth activity, as, for instance, pigmented nevi. Conversely the hereditary freedom from cancer may be due to a lack of tendency toward such diseases as predispose to cancer. Thus it is probable that the absence of gastric cancer in the Indian is in part due to his freedom from such gastric diseases as predispose to cancer. This hereditary variability in the liability of tissues to respond to proliferative stimuli may in certain cases perhaps be caused by variations in the amount of "sensitizing" substances which have the property of making tissues, which would otherwise have been inert, to an unusual degree responsive to various growth stimuli, which in themselves may have only a very restricted intensity. Thus we have shown that normally the corpus luteum substance sensitizes the tissues to the action of otherwise indifferent mechanical stimuli. Perhaps in different individuals the production of the ovarian hormone which stimulates the proliferative activity of the mammary gland differes in strength or quantity. These represent at the present problems which are not yet solved, but seem to be accessible to an experimental attack.

On the whole we may conclude that in all probability the character of hereditary factors is not different from other causes leading

to cancer. They seem to consist in the presence or absence of chemical or mechanical growth stimuli which originate within the organism, and which, while in themselves they are often not able to produce cancer, do so if combined with other growth-promoting factors. We must include in this category conditions which make tissues receptive, sensitize them to the action of mechanical or chemical growth stimuli. Such conditions may perhaps originate through a mutation localized in a chromosome. Thus Miss Stark has observed in the fly Drosophila a hereditary localized abnormality of growth which showed a certain resemblance to tumors in vertebrates. Boveri went so far as to explain changes in the chromosomes in the nuclei of somatic cells as the only cause of cancer, irritation and inflammation acting only indirectly in calling forth changes in the distribution of chromosomes which cause excessive tumor growth. While we must indeed assume that the hereditary factors in cancer are localized primarily in the chromosomes and that in those changes in proliferative and motor activity which constitute the cancerous transformation changes in the nucleus and particularly in the chromosomes may be involved, some experimental facts can hardly be reconciled with Boveri's generalization. I refer, for instance, to the gradations in cancerous transformation which have been shown to exist, to the quantitatively graded effect of internal secretion, to the contact-combination tumors, to the necessity of long-continued stimulation which is so noticeable a feature in the origin of most cancers as contrasted, with the readiness with which abnormalities in chromosome distribution can be brought about through single experimental interferences.

(*d*) *The embryonal character of tissue or disturbances of embryonal development and parthenogenetic development of ova* in the ovary play essentially a predisposing role in the origin of cancer. They provide a substratum which has a greater tendency to proliferate and is more receptive to abnormal growth stimuli which may reach it. We know that cancer which is once established grows better in young than in old individuals. The young tissues grow more actively than older tissues, and in addition the body fluids in younger organisms are more favorable to proliferating tissues than those of older individuals.

Embryonal tissues which begin to develop under abnormal conditions are thereby exposed to abnormal stimuli and thus may in certain cases be transformed into cancer. It is characteristic of many cancers whose origin is embryonal that their constitution is complex, they being usually composed of more than one kind of proliferating tissue. Especially in the germ glands, but also elsewhere, they may resemble malformed embryos, certain parts of which assumed a malignant growth. It has been suggested by various authors that such complex teratomata which are found in so preponderating a number in the sex glands may owe their origin

to a parthenogenetic development of ova. There was, however, some difficulty which prevented the general adoption of this view. There was not known any case in which the egg began to develop spontaneously within the ovary, particularly in mammals. The large majority of pathologists inclined therefore rather toward the adoption of the Bonnet-Marchand hypothesis that such teratomata are due to aberrant blastomeres.

Within recent years, however, we have succeeded in demonstrating that a parthenogenetic development of the egg in the mammalian ovary may actually occur. We have observed such a condition in a considerable number of cases in the guinea-pig. While parthenogenesis usually leads to the formation of embryonal placenta, thus explaining the occurrence of chorion epitheliomata in the sex glands, in two cases the production of typical embryonal tissue in the more restricted sense has been observed by us. There can therefore be no doubt that parthenogenetic development of the mammalian ovum within the ovary does actually take place and that it is a relatively not rare occurrence in certain species. This provides a basis of fact for the interpretation of embryonal tumors in the germ glands as being due to parthenogenetic development of ova within the follicles. There exists, however, a difference in different species in the readiness with which eggs mature in the ovary, such a maturation being apparently common in the guinea-pig and difficult in the rabbit. We may therefore expect that the frequency with which ovarian teratomata are found should vary in different species. In guinea-pigs we could show that such parthenogenetically developing ova do usually not change into teratomata such as they have been observed in man, but that they are invaded and gradually superseded by the host connective tissue before they have had a chance to develop into tumor-like masses.

It has now furthermore been established that an extensive migration of germ cells within the embryo takes place at an early stage of development. Thus it is conceivable that some of the embryomata which we find in places far removed from the ovary may be due to such a migration of germ cells which failed to reach their proper place.

There can, however, be little doubt that not only eggs but also parts of the embryo may, as a result of abnormal conditions, develop abnormally and give origin to teratomata and mixed tumors. It has usually been assumed that a detachment of embryonal cells from their normal environment is necessary for this purpose. Especially the recent investigations of Werber and Stockard have shown that even without such a separation, through toxic action (Werber) or a mere retardation in development (Stockard), embryonal parts whose development is usually coördinated may become independent of each other and may at relatively late stages of embryonic development give origin to twin

and monster formation. Thus we may assume that abnormal metabolic processes or other conditions which retard development at a certain place and at a critical period of development may cause embryonal malformations, teratomata or mixed tumors. But neither parthenogenetic development as such nor the formation of embryonal abnormalities through a slowing down of development can in themselves sufficiently explain the origin of cancer. Embryonal tissues which have been experimentally separated from their normal environment through transplantation behave in certain respects like normal embryonal tissues. They grow rapidly, differentiate and with progressive differentiation their development becomes slower; at last it ceases, and now the host tissue invades the transplant and a retrogression of the embryoma sets in. Askanazy, however, observed three cases in a series of approximately 150 experiments, in which the embryomata in the rat developed into cancers. These three cases were experiments in which the embryomata had persisted in the host for a much longer period than they usually do after transplantation. We may assume that in these cases abnormal stimuli had a chance to act on the embryonal tissues. Abnormalities in embryonal developement or parthenogenesis as such are not sufficient to produce cancer; they merely prepare a favorable substratum on which additional stimuli may act. And it is the latter which call forth the development of cancer in these cases.

It is possible that in certain cases a changed environment as such may supply the stimulus which is needed in order to increase and prolong the proliferation and migratory energy of embryonal cells. In mammals, as we have seen, subcutaneous or intraperitoneal transplantation does not usually supply a sufficient stimulus for embryonal cells. If very early embryonal stages are transplanted they perish in the large majority of cases; but in one case we succeeded in the guinea-pig in producing thus the beginning of a peritoneal pregnancy.[1] Now, mammalian embryonic cells are adapted to growth within a living host organism. In animals in which the embryos develop normally outside the body, transplantation into an adult animal might perhaps supply a change in the environment large enough to produce profound stimulation of the cell activities. Experiments have, however, shown that in birds embryonic transplantations produce the same result as in mammals. Just as through transplantation in the rat and mouse, so through transplantation in birds embryomata are produced which have only a temporary existence. In amphibia, on the other hand, according to the recent experiments of Belogolowy,[2] injection of embryos in an early stage of development does not lead to the

[1] Loeb, Leo: Proc. Soc. Exper. Biol. and Med., 1914, No. 3, vol. xi; Biol. Bull., 1915, xxviii, 59.

[2] Belogolowy, G.: Archiv f. Entwicklungsmechanik, 1918, xliii. (It has been impossible for us to procure the original paper.)

development of typical embryos, but in certain cases to monstrosities. Various tissues proliferate irregularly and independenly of each other. Plasmodia and irregular cells, not unlike sarcomatous cells, may penetrate into the host tissue and destroy the host organism as late as five or six months after transplantation. Here, apparently, certain similarities to cancerous growth are obtained. Whether a real cancer was produced, whether the growth energy continued undiminished without any farther differentiation, cannot be determined on the basis of the incomplete report of this work which is at our disposal. It is possible that in contact with the tissues of an adult organism cells which are in an early stage of embryonal development become transformed into plasmodia and syncytia and penetrate into the host, in a way similar to that we have described in the case of parthenogenetically developing eggs within the ovary. At that time we came to the conclusion that it is the contact with strange tissues which causes the transformation of embryonic cells into embryonal placenta.[3] It is possible that under the influence of the stimulus of the strange environment a similar transformation takes place also in amphibian embryos and that the infiltrative growth continues and that thus a growth resembling in its effects a chorioepithelioma may be produced. At the same time the strangeness of the environment may, in so far as it does not lead to the destruction of the tissue, produce a desequilibrization, a severance of the mutual connections which exist between constituents of the embryo and which normally coördinate the development of parts to a whole, and thus duplication of certain parts of the embryo, similar to the result obtained in embryos through the action of certain poisons or through changes in temperature, may be brought about.

(*e*) *Age.* The relation between the age of the individuals and the frequency of cancer is not as simple as it is often assumed to be. Cancer may appear in young individuals. This is especially the case in those cancers which are due to transformation of embryonal into cancerous tissues. In some cases, however, the period of latency of these tumors may be considerable. The majority of those tumors which are due to stimulation of adult tissues appear in later life; this holds good in the case of human as well as of animal cancers. Thus we found in a statistical study of cancer in cattle, which we undertook twenty years ago, that the large majority of these cancers appeared in old cows. In mice also the incidence of mammary cancer increases, on the whole, with increasing age. This rule, however, does not preclude the fact that in man as well as in animals these same tumors may appear at a very early period of life. The number of mammary cancers which is found in young mice is indeed very considerable. The age at which the incidence

[3] Loeb, Leo: Arch. f. Entwicklungsmechanik, 1911, xxxii, 662.

is greatest differs furthermore in the case of different strains of mice and this age character is just as much inheritable as the frequency of cancer in a particular strain. The age curve of frequency of cancer differs also in the case of different kinds of cancer. The age factor has therefore only a subsidiary significance in the etiology of cancer. The probability that long-continued stimulation leads to cancerous transformation must, of course, increase with increasing duration of life of the individual. Thus cancer must become more frequent with increasing age notwithstanding the better conditions for growth which young organisms and tissues offer. Cancer has this characteristic in common with many other diseases, where likewise the incidence increases with increasing age and the mortality as a whole shows a similar curve.

There is, however, still a problem concerning the age incidence of cancer which awaits solution. We have seen that it is accumulation of physical or chemical stimuli which causes cancer. These stimuli may originate in the outside world or in the inner environment of the cells within the individual. We have shown experimentally that in the case of these inner chemical stimuli (internal secretion) the quantity of the stimuli which is active in a given time may influence the cancer age. In part then we may refer the cancer age to the action of the environmental stimuli. It is, however, possible that in addition changes within the tissues which are characteristic of old age may tend to enhance the chances for cancerous transformation. It may be, as I pointed out on a previous occasion, that the changes characteristic of old age may place the cells into a new environment. Horst Oertel expresses the view that cells which are injured might be especially liable to undergo cancerous transformation, and Goodpasture has recently drawn attention to the frequency with which multiple tumors appear in dogs which have reached old age. At present we must regard it as problematical whether in addition to the cumulative action of external stimuli such internal factors play a part in the origin of tumors. If old age changes should bring about such an effect, an environmental change would in this case act as a growth stimulus. The environmental change which would produce such a transformation and lead to a proliferative reaction on the part of cells, may or may not have an injurious effect on the cells which it influences. If it should have such an injurious influence, it would be an adventitial, not an essential connection. Indeed, if these injurious by-products of the interference exceed a certain limit, the proliferative response of the tissues does not occur. Most of the tissues are constituted in such a way that within certain limits changes of environment of various kinds do not depress the cells but call forth a response which indicates increased activity.

(*f*) *Contact of normal tissues with cancerous tissue* may cause the transformation of the former into cancerous tissue. Thus may be

produced what we designated as "contact-combination tumors." Such a transformation of normal into cancerous cells in contact with cancerous tissue has been observed in the case of spontaneous tumors of man and animals as well as in the case of transplanted cancers. Primary carcinomatous tissue has called forth in many cases the transformation of connective tissue into sarcoma and in some cases the transformation of adjoining normal epithelium of a different kind into carcinoma; thus "combination tumors" originated. Ehrlich published such an observation more than twelve years ago. At the same time we observed sarcomatous transformation of stroma after transplantation of mammary carcinoma in waltzing mice as early as in the first generation of the transplanted tumors, and subsequently in another case we found a transformation of epidermis into squamous-cell carcinoma in contact with a mammary carcinoma. Some authors believed that the tissue which had been interpreted as sarcoma, was only a pseudosarcoma, and consisted in reality of spindle-shaped epithelial cells. However, there cannot be any doubt that in such cases we have actually to deal with a proliferation of true fibroblasts, and in accordance with this interpretation is the recent observation of Woglom, who found the formation of cartilage in such a contact-combination tumor.

We have certain analogies for such contact action in the case of embryonal and also of adult tissues. Thus substances given off by the optic disk may call forth proliferation of the epidermis with which it is in contact, the proliferating cells giving origin to the lens. In the mammary gland the condition of the stroma depends upon the state of activity of the gland tissue. Activity of the gland tissue produces a stroma rich in fibroblasts and a resting gland induces a fibrous transformation of the stroma. Around gland ducts which are metabolically relatively inactive, the stroma is usually fibrous. It is therefore probable that the cancerous transformation of normal tissue in contact with cancer is another instance of the stimulating effect which one tissue may have upon another normally. The difference in the normal and pathological cases is mainly a quantitative one.

(*g*) *The Possible Significance of Microörganisms in the Etiology of Cancer.* When microörganisms were discovered as the cause of infectious diseases, some of which were associated with a noticeable tissue proliferation and with the formation of secondary foci, comparable to metastases, and when it was shown that certain microorganisms can call forth even proliferation of epithelial structures, the conclusion was drawn that cancerous growth may likewise be due to microörganisms. This conclusion seemed to be confirmed by the presence within the tumors of structures which resembled various unicellular microörganisms. Another fact which seemed to

point in the same direction was the so-called endemic occurrence of cancer in certain animals. It was referred to cage infection.

At present neither of these arguments is accepted, at least so far as the large majority of pathologists is concerned. No unicellular microörganisms have been found in cancer; no agent can be separated from cells in mammalian tumors. The structures taken to be parasites were shown to be due to cell degenerations and phagocytoses. The endemic occurrence of cancer is due to two factors: (1) to the hereditary transmission of cancer in certain strains of animals, and (2) to the introduction of metazoic parasites which infect a certain class of animals at a particular place and act as a temporary stimulus of the tissues, and which later disappear after the tissues have been converted into cancer. This applies, for instance, to the cancer in rats observed by Fibiger.

The arguments which speak against the significance of microorganisms in the etiology of the large majority of mammalian tumors seem to be convincing. Observation shows that human cancer is in many cases due to the long-continued action of growth stimuli on cells. Occasionally a growth stimulus may call forth the sudden appearance of cancer. Experimentally cancer has been produced through the action, physical or chemical, of growth stimuli and has been prevented through the withdrawal of chemical growth stimuli (mammary cancer of mice). It has been shown that no immunity can be produced against auto-cancers (spontaneous cancers) but only against homoiocancers (transplanted cancers). Immunity against homoiocancers can be produced through normal tissues of the same species. These facts prove that we have in these cases to deal not with an immunity against an extraneous organism but against tissues growing abnormally.

Through the action especially of chemical growth stimuli normal tissues can be transformed into cancerous tissues without the intervention of ulceration. Injection of any known microörganism does not produce cancer. It is therefore extremely improbable that the cancers which originate after long-continued stimulation of normal tissues should be due to the accidental invasion of the tissues by a class of microörganisms which have not been observed at places where they would have to enter the tissues, and which would have to be ubiquitous, in view of the great number of animals which can be made to be cancerous. We would, moreover, have to assume that specific microörganisms exist in the case of different varieties of tumor in view of the fact that cancer has to some extent a specific character. Such microörganisms should, moreover, be able to gain access to the embryonal tissues which form in a certain number of cases the matrix of the tumors. All these considerations make it very improbable that in addition to the causes of cancer enumerated above there are other factors, which while leading a hidden existence would be the really important ones, in contra-

distinction to the aforementioned causes which would only serve as an opportunity for the microörganism to enter the host tissues.

Yet it is conceivable that the same kind of cancerous growth which is produced through a change in the chemism of the cell as the result of the long-continued effect of growth stimuli, might also be called forth through the action of an extraneous stimulus constantly associated with the cells; such a stimulus might be furnished by a substance given off by a microörganism. There are certain sarcomata of fowl in which Peyton Rous discovered an agent separable from the tumor cells through filtration and other means which had failed in the case of mammalian cancers. Injection of these agents into other fowl causes the development of tumors identical with the original ones. These tumors are metastasizing and transplantable. After transplantation of tumor tissue transplanted cells remain alive and give origin to the new growth. An immunity against these tumors can be produced, but it is an immunity against the agent and not against the tumor cells, in contradistinction to the immunity obtained in the large majority of other and particularly of the typical mammalian tumors, where we have to deal with an immunity against tumor cells. Certain sarcomatous tumors found in hares and perhaps a certain sarcoma found in dogs resemble in certain respects the chicken sarcoma, and although a direct separation of tumor agent and tumor cells has not been accomplished in the latter cases, the etiology may be similar.

In the case of the fowl tumor the agent seems to be specifically adapted to the organism of fowl or of birds in general. In this sense we are inclined to interpret the fact found by Rous that only in certain birds and not in rabbits is it possible to produce an immunity against the agent of the chicken sarcoma. It is not improbable that in the case of these sarcomata we have indeed to deal with proliferative processes called forth by microörganisms accompanying the cells and specifically adapted to the latter, although the possibility cannot yet be quite excluded that the agent may be a substance produced by and separable from the proliferating cells.

In plants Erwin Smith has discovered a bacterium which causes a gall to assume invasive properties.* This bacterium acts through the production of an apparently simple substance which induces the proliferation of the plant cells.

It is therefore possible that while in the majority of cancers often repeated stimulation of tissues leads to a long continued or even perpetual increase in the intensity of those metabolic processes which cause cell proliferation and cell movements, in certain sarcomata the same effect is produced through a constantly acting extraneous chemical growth stimulus, supplied by microörganisms and not as in the case of the majority of cancers through the own metabolism of the cancer cells.

Some General Considerations. We have seen that all the factors which in various ways either by chemical or physical means increase the proliferative energy of cells may act as causes of cancer; these conditions are not different from those growth stimuli which lead to regenerative and what might be called correlative growth in normal tissues; added to these factors are in certain cases factors residing within the cells, which make these cells more responsive to outer growth stimuli, thus providing a sensitization which in other cases is furnished by sensitizing substances carried to the cells from other organs. We concluded that in order to lead to the formation of cancer in many cases several of such factors must coöperate. Some of these factors are hereditarily transmitted in a certain graded quantity from generation to generation, while the other factors are variable and extraneous. All these factors have one characteristic in common: They all increase the growth energy of normal tissues either directly, or indirectly, the latter by sensitizing the tissues to the action of growth stimuli.

We have previously shown experimentally that a combination of such diverse growth stimuli can under certain conditions accomplish results which are very much greater than the ones produced by either of these factors alone. In the case of the maternal placenta two factors coöperate. In the first place a substance is given off by the corpus luteum. It calls forth only a very slight proliferation of the uterine mucosa, but it sensitizes the latter in such a way that the subsequent application of an external stimulus (a foreign body, ovum), which in itself would likewise call forth only a very slight reaction, leads to the production of tumor-like masses, placenta and placentomata (deciduomata). In a similar way heredity might in some cases act by supplying sensitizing substances which make cells receptive to the effect of outer growth stimuli. Thus in xeroderma pigmentosum we find an abnormal sensitiveness of the skin to the action of outer stimuli, probably light, which causes a sequence of changes leading ultimately to the production of cancer and not unlike those observed in experimental cancer in animals.

There is some reason to assume that a reciprocal relation exists between those factors which may be classed as hereditary and those which are extraneous growth stimuli. It may perhaps be expressed through the formula $H + S = C$, where H represents hereditary factors and S external growth stimuli. The greater the quantity of one kind the less is needed of the other kind in order to produce cancer. Thus it seems that roentgen rays can ultimately produce cancer in all persons whether or not they are hereditarily predisposed to cancer, provided the roentgen rays have a chance to act over a sufficiently long period of time. Of course as far as the quantitative aspect expressed in the equation is concerned we have at present to deal merely with a hypothesis. We found that given a certain hereditary predisposition a quantitative relation seems to

exist between the amount of internal secretion given off and the frequency of cancer which resulted. In this case a quantitative relationship is not merely assumed, but has been definitely proved.

We conclude that various growth stimuli including those of a regenerative character may gradually bring about a change in the cell equilibrium. The normal cell equilibrium which is characterized by a definite proliferating energy may pass through several transitional stages into an equilibrium of greater proliferative and kinetic energy. This is not only a change in intensity but also in duration. In the last stage the change has apparently become permanent.

In the normal organism we find a complex interaction of various tissues. They exert upon each other under certain conditions a restraining and under other conditions a stimulating effect.

Alteration of these relationships and introduction of an abnormal environment leads usually to only temporary changes in the cell equilibrium, to growth processes of a regenerative or correlative character; this applies to changes affecting embryonal as well as adult tissues. But through frequent repetition of these changes which act as stimuli the cell equilibrium may be changed in such a manner that the alteration continues over a long period of time or has become permanent. In different cases the quantity of stimulation which is needed for this effect to take place varies. We may call such a change in cell equilibrium, inasmuch as it is transmitted to successive cell generations and may appear as a well-defined transformation in the character of the cell, a mutation, but it would be a mutation of somatic cells. This somatic mutation is, however, in part at least, dependent upon conditions transmitted through the germ cells.

The basis of this transformation in cell equilibrium may be conceived as a change in cell metabolism, during which substances are produced which maintain the alteration in cell metabolism on which the acceleration in growth and the increase in motility depends. It is conceivable that in certain cases a similar constant alteration is produced through a stimulus reaching the cell from an extraneous source; a microörganism might perhaps be able to supply such a stimulus.

The various kinds of transitory increase in growth and kinetic energy as exemplified in regenerative, embryonal, correlative growth and in the combination of correlative and regenerative growth (the development of deciduomata) are probably the expression of a kind of metabolic cell change similar to the one observed in cancer. And tissues in which correlative or regenerative growth processes occur are therefore liable to become cancerous, while those which are not accessible to the former are not likely to undergo the cancerous transformation. There are, however, differences in intensity and also differences of a secondary character between the kinds of normal increase in growth energy and between

cancerous growth. In the latter, as the result of the abnormal conditions in the cells which are reached by the stimuli, structural abnormalities are produced.

We have attempted to correlate the most important facts which have a bearing on the etiology of cancer. We see that while of a composite character the various factors, as far as they are known to us, have one characteristic in common: they tend to increase the proliferative energy and motility of cells which are not yet cancerous. The picture thus presented is more complex than the one which we meet in the "theories of cancer" to which so much attention has been given in the literature. In the case of a "theory of cancer" usually one or the other of the factors underlying cancer has been considered with the exclusion of all the factors. Deductions based on the histological characteristics which were usually not accessible to experimental analysis formed often the basis of such theories. Thus a simplification was attained which was more apparent than real.

Equally prominent in the literature has been the discussion whether or not a certain new formation is to be classed as a cancer. The answer given usually depended on the "theory of cancer" to which the author subscribed. A definition of a condition cannot be more definite than our knowledge of this condition; otherwise the definition produces an artificial restriction to the search for new relations. A definition is therefore perhaps of less importance than is often attached to it. It is essentially a summary of our knowledge of a phenomenon. Cancer is abnormality of growth. Primarily it is a disturbance in the equilibrium of the individual, not through toxins but through an increased proliferative activity of the cells which is usually associated with an increased motility. This increase is long continued and often permanent. It is in all probability in the large majority of cases due to changes in cell metabolism, which are of such a character that they propagate themselves. In some cases the same effect may perhaps be produced through extraneous causes, such as microörganisms.

THE TREATMENT OF THYROID AND OTHER ENDOCRIN DISTURBANCES AS VIEWED BY THE INTERNIST.[1]

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Mrs. G. C., a farmer's wife, aged fifty-nine years, was brought to the hospital by her family physician. She complained of a throb-

[1] Read before the Section on General Medicine of the College of Physicians of Philadelphia, December 15, 1919.

bing, beating sensation in the abdomen and also of general weakness. These symptoms came on gradually in the past six months. They had their inception apparently from a nervous shock. The patient's only son had died rather suddenly following an operation for a ruptured appendix and a few days later her only grandchild died of influenza. On further inquiry it was found that nine years previously, while the patient was passing through the menopause, her only daughter died very suddenly, and that following this death she had what was then called a "nervous breakdown," a condition thought to be similar to her present attack.

The patient was found to be 37 pounds below her usual weight. The skin was moist. The pulse-rate was 132 and easily accelerated; the heart action was violent. There was tremor of the tongue and hands. The hair was brittle and the eyes prominent. A slight bogginess of the isthmus of the thyroid could be felt. Practically every symptom of hyperthyroidism was present.

This is a familiar picture which resulted from the tragic episodes which came to the household over which the patient presided. In a rather intensive study of the case, definite evidence of an unbalanced endocrin system in which the thyroid gland was the chief factor was found. In addition to the very evident symptoms the examination brought out the fact that carbohydrate metabolism was disturbed. A subcutaneous injection of ½ c.c. of 1 to 1000 adrenalin solution ("Goetsch test") produced a glycosuria, though it aggravated the thyroid symptoms only slightly. A carbohydrate tolerance test also brought sugar to the urine, even though there was no previous hyperglycemia demonstrable. While the patient was resting in her changed surroundings the thyroid lost its boggy feel, body weight was increased and the most prominent symptoms, especially the tachycardia and anxiety, disappeared.

This patient, aside from illustrating a large and increasing group of cases, also demonstrates how profound and disabling such symptoms may be without there being present very definite physical signs suggestive of definite pathology; and it also brings out the question whether there might not be an early stage in the course of the disturbances of the endocrin system, where a comprehension of what is taking place, or is about to take place, may lead to earlier recognition and consequently more satisfactory treatment. It is for the purpose of presenting this idea that the present consideration from the viewpoint of the internist is attempted.

It is, of course, axiomatic that if a disease is to be recognized and dealt with at its earliest inception there must exist a thorough knowledge of the etiology as well as of the pathology and of the clinical manifestations. Unfortunately of diseases and disturbances of the endocrin system we know comparatively little, practically nothing definite, of the etiology, and we have only confused ideas of the associated pathological processes. Compared with our present-

day knowledge of such a well-known disease as typhoid fever we know very little about the diseases of the glands of internal secretion, and are therefore at a great disadvantage and no doubt show a great confusion of opinions. There is not yet that coördination in effort and ideas of the laboratory workers, of the clinician and of the surgeons, all of whom are intensely interested in the problems which the subject presents. In the last decade or so much information has accumulated: (1) Because of the fact that endocrin disturbances are more generally recognized by the clinician; (2) their relation to disease in general and to definite pathology is being established, and theorizing has been displaced by more earnest laboratory investigation. The recent great war with all its strain and anxiety, resulting in so-called shell-shock, effort syndrome, neurocirculatory asthenia, all of which may be manifestations of endocrin disturbance, has made the problem really acute, and it is well to pause at this time for a moment to review the present status and to consider the foundations for our faith in the procedures we are advocating when we speak of the treatment for a certain symptom-complex referred to the endocrin system. In this consideration the diseases and disturbances of the thyroid gland are of particular importance.

In such a review we must acknowledge our debt to the laboratory worker and his discoveries. It will be interesting, and probably helpful, to refer briefly to some of their epoch-making revelations, because from them will be seen at once the relation which the several glands of the endocrin system bear to each other, and it will also show where the clinician receives his greatest help and in what direction his efforts will likely prove most fruitful. Only brief reference can be made to early laboratory results which have more recently shown the coördination of the endocrin system and how delicately this system is balanced.

The Suprarenals and Their Specific Secretion. It was in 1841 that Magenda told his students that he had nothing to say about the suprarenal bodies, because the capsule is no longer considered as a secreting body. Just fourteen years later (1855) Thomas Addison described the disease which bears his name, and this marked the beginning of clinical work in relation to the suprarenal glands. In 1902 J. Takamine published the work of Aldrich and himself,[2] giving a description of a crystalline compound and its clinical formula, which they isolated from the suprarenal gland. Later, Stolz, followed immediately by Abel, produced this crystalline form—adrenalin—synthetically. This substance figures largely in developing our knowledge of the interrelation of the ductless glands. With it we can produce most profound circulatory disturbances: can, under certain conditions, activate the thyroid gland and can

[2] Jour. Am. Med. Assn., January 18, 1902, p. 153.

unbalance carbohydrate metabolism. It has become a definite therapeutic agent and, administered under certain conditions, also gives diagnostic information.

THE THYMUS GLAND AND ITS RELATION TO THYROID DISTURBANCE. In his Harvey lecture in March, 1914, Halstead called attention to the belief that the thymus gland plays an important part in Graves's disease. He said: "It has been estimated, as a result of non-operative clinical examination, that in about 40 per cent. of all cases of exophthalmic goiter the thymus is present." He refers to 500 patients with Graves's disease operated with approximate cures in 60 per cent. The exophthalmos and the typical blood picture seemed the most difficult conditions to overcome, even when the major symptoms had largely subsided, but both conditions yielded when the thymus was considered properly. Halstead then refers to the relation of the thymus to the thyroid as noticed by other observers, and says, from the facts gleaned at the autopsy table, from experiments on animals and above all from the results following primary thymectomies, we have convincing evidence that the thymus gland may play an important part in Graves's disease. Two months later he referred to the treatment of the thymus gland with roentgen rays in certain selected cases of Graves's disease and reported his experience in a subsequent paper. While the coördination of the thymus and the thyroid glands, which Halstead suggested, has not proved so generally convincing as it promised, his work led to the demonstration of the effect of the roentgen rays in thyroid disease, whether through the thymus or direct on the thyroid.

An interesting case which occurred in my experience, apparently bearing upon the relation of the thymus to the thyroid, is as follows: A man whom I had known for a number of years consulted me about five years ago on account of a tickling in his throat. A physical examination showed nothing, but rather definitely prominent eyes. An examination by a nose and throat specialist was negative. The hacking cough continued, however, and was finally so severe that the patient could not lie down without bringing on a violent paroxysm of coughing. He was unable to sleep in a prone position. About this time he had a severe attack of acute tonsillitis, which was followed by tachycardia, which could not be explained except as probably due to the preceding acute infection. Graves's disease was considered, as many symptoms were suggestive. The thyroid, however, was not enlarged. A roentgen-ray examination of the chest, especially of the mediastinum, showed an enormous enlargement of the thymus gland. It is possible that this was present in a lesser degree from the first and accounted for the hacking cough. It was suggested that the acute infection led to a rapid enlargement of the thymus and that the symptoms of Graves's disease, which we then recognized clearly, were due to the effect of the thymus upon

the thyroid. The symptoms, including the tickling cough, were relieved entirely by treating the thymus with roentgen-ray applications. The patient has been well now for nearly three years. A roentgen-ray examination of the mediastinum following the treatment showed a great reduction in the thymus gland. The excellent result in this case is another reason for reporting it. It is possible that the roentgen-ray applications to the thymus had a direct action upon the thyroid as well, and that the change in size of the thymus was simply coincident. I am all the more willing to consider the case in this way since reading the recent article by Drs. Edward Park and Roy D. McClure[3] in which they conclude, from an extensive review of the literature and after painstaking animal experimentation, that destruction of the thymus function fails to show an effect on the thyroid gland. While the thymus may not bear the relation to the thyroid which Halstead suggested, after all his work called attention to the effect of the roentgen rays upon the thyroid secretion, and added greatly to the therapeutics of thyroid disease.

THE PITUITARY BODY AND ITS SECRETION. The work of Marie, of Schafer and later of Howell called attention to the hypophysis cerebri, in the chain of the glands of internal secretion, as a "vitally important organ." It was not, however, until the masterly work of Cushing[4] appeared that it was at all appreciated what pathology may occur in the pituitary gland, and what clinical and what physiological disturbances may follow. There resulted from the studies of this gland, as from that of the suprarenal, another addition to our therapeutic armamentarium. The effect of pituitrin upon the gravid uterus and upon the relaxed unstriated muscles in general is well known. More recently the effect of pituitrin on urinary secretion has been brought to our attention. A striking demonstration of the effect of pituitrin on diabetes insipidus is presented in the following case: A sixteen-year-old girl consulted me on account of sleeplessness and of being occasionally mentally confused. In the course of the history it was found that the patient had a polyuria, passing as much as 5 liters of urine in twenty-four hours. She also had polydipsia. This was largely responsible for the sleeplessness. After careful investigation a diagnosis of diabetes insipidus was made. Pituitrin was given daily and in forty-eight hours the urinary output was reduced to 1½ liters. The intense thirst disappeared and sleep was natural. The symptoms were later controlled by smaller doses given less frequently. The limitations of this treatment are, of course, generally recognized, and yet it is a good example of the profound specific effect of a substance elaborated in the hypophysis cerebri. In an article in the *Quarterly Journal of Medicine* (April, 1919), Kenneway and Mottram, of the Middlesex

[3] The Results of Thymus Extirpation, Am. Jour. Dis. Children, November, 1919.
[4] Bull. Johns Hopkins Hosp., May, 1910.

Hospital, London, recorded the antidiuretic effect of pituitrin subcutaneously injected in normal individuals as well as in those having diabetes insipidus. It would seem, however, that this observation will need further investigation.

THE PANCREAS AND ITS INTERNAL SECRETION. The role of the islands of Langerhans in relation to carbohydrate metabolism, and especially the histological changes which take place in diabetes mellitus, was first definitely brought to our attention by Opie in 1900.[5] Since that time the work upon the pancreas has been prodigious and has resulted in a more rational view of the relation of diabetes mellitus to the pancreas. McCallum[6] called attention to the actual hypertrophy of the isles in severe cases of diabetes mellitus. And later Allen[7] demonstrated definitely the relation between the disease of the pancreas, especially of the isles of Langerhans, and diabetes mellitus, and suggested a rational treatment, which Joslin, from a clinical standpoint, subsequently made practical. Allen and Joslin's work is intensely practical and is of real value to the clinician. The emphasis which Allen has put upon early recognition of physiological disturbance of the isles of Langerhans and prompt definite interference is applicable not only in diseases of other organs of the endocrin system, but may be of value in those diseases in general whose early symptoms might be easily overlooked.

It would be interesting to speak of the ovaries and their specific secretion, of the parathyroids and of other glands of the endocrin system, but I shall now direct my remarks more specifically to that laboratory work which has led the internist to more rational procedures in diseases and disturbances of the thyroid gland. The first description of thyroid disturbance by Graves, in 1835, is, of course, a matter of history, and the laboratory work which led to the extraction of a substance from sheeps' thyroid, which when given in sufficient dose reproduced the symptoms of Graves's disease. The important place which thyroid extract took as a therapeutic measure is well known to all. Very little of value has been added to the definite clinical description which characterizes Graves's first paper. I shall refer only to the recent laboratory investigations and their bearing upon our present concept of thyroid disturbances, especially in so far as early diagnosis and the treatment therefor is concerned.

THE DISTURBANCE OF BASAL METABOLISM IN HYPERTHYROIDISM. We are indebted to Du Bois[8] for first successfully calling attention to the striking change which takes place in metabolism in the thyroid case. In his paper Du Bois says that in a study of the basal metab-

[5] Jour. Exper. Med., 1901.
[6] AM. JOUR. MED. SC., 1917, cxxxiii, 432.
[7] Glycosuria and Diabetes, Harvard University Press, 1913.
[8] Arch. Int. Med., 1916, xvii, 915.

olism in hyperthyroidism it becomes apparent there is an increase in metabolism in proportion to the severity of the disease. Very severe cases show a metabolism 75 per cent. or more above the average, severe cases 50 per cent. or more, moderately severe and mild cases show an increase of less than 50 per cent., while a few mild and several atypical cases, or cases in which operation has been performed, are within normal limits. The degree of tachycardia, goitre, exophthalmos and mental irritability are roughly proportional to the increased heat production. At least a part of the tachycardia is due to the increased metabolism, and perhaps it might be possible to reproduce the extreme tachycardia, the cardiac enlargement, emaciation and mental irritability if we are able to stimulate the metabolism of normal men for twenty hours a day over a period of months or of years.

These observations of Du Bois and his conclusions have become so generally recognized that it is now necessary to make metabolism observations before a diagnosis of hyperthyroidism is accepted, or at least before a reliable and safe prognosis can be made. It would be interesting to note, by a series of investigations, whether the basal metabolism is changed in any way in those early cases in which the subcutaneous injection of adrenalin seems to develop a so-called potential hyperthyroidism. Studies in metabolism are now being made in the cases of so-called effort syndrome which may result in differentiating these cases definitely from hyperthyroid cases or which may show that they manifest early symptoms of the exophthalmic goitre syndrome. I am of the opinion that the latter may be found the true interpretation, though I believe this is contrary to the opinions of those who have had large opportunity for observation in the neuropsychiatric division of the army.

Barring the slight temporary bogginess of the thyroid, the case to which we referred at the beginning of this paper, came very near corresponding to the neurocirculatory-asthenia syndrome instead of to that of hyperthyroidism. It will require more definite laboratory and clinical work before this point of differentiation can be clarified.

The Innervation of the Thyroid Gland. This was presented in an article by Cannon,[9] entitled "Conditions Affecting the Secretions of the Thyroid Gland," in which he concluded, after describing his methods of observation, that "The nerves distributed to the thyroid cells belong to the sympathetic and not to the vagal supply and that their effects are not indirect through alterations of blood flow: indeed, that they are true secretory nerves. The thyroid gland is subject to that division of the nervous system which is brought into action in emotional excitement and which causes adrenal secretion. It is probable, therefore, that the thyroid, like the adrenal,

[9] Boston Med. and Surg. Jour., 1916 clv, 562.

has, normally, functions which are performed in times of critical emergency. It may be that such an emergency function is an exaggerated form of the routine activity of the gland." Cannon's work has been severely criticized, but it has stimulated research on the innervation of the thyroid and will no doubt result in bringing out the real facts, which is, of course, the object of all scientific investigation. The latest word on this subject is probably that of C. A. Mills,[10] in which he affirms the lack of secretive function of the sympathetic fibers of the thyroid gland.

THE ISOLATION IN CRYSTALLINE FORM OF AN IODIN COMPOUND FROM THE THYROID GLAND. In an article by Dr. E. C. Kendell, of the Mayo Clinic,[11] he announces the discovery and separation among other substances, of a purely crystalline compound containing 60 per cent. iodin. It appears to be an iodo-di-hydroxy-indol. Administration of this substance in a human being produces a rapid increase in pulse-rate, gain in vigor and increase in metabolism and nervous irritability. Given in excess, toxic symptoms are produced. The amount of iodin compound required to produce toxic effect is exceedingly small. He believes it plays an important role in the production of the symptoms of exophthalmic goitre. Kendell says, further, that in exophthalmic goitre two abnormal conditions exist: (*a*) The secretory capacity of the gland is greatly increased, and (*b*) the reservoir capacity of the gland is greatly decreased.

The use of iodin in goitre is a procedure to which our attention was called many years ago. The results of Kendell's work impress one very much with Marine and Kimball's observations, as reported in the *Archives of Internal Medicine*, July, 1918, "The Prevention of Simple Goitre in Man." They had the opportunity of observing 1080 girls in the Akron public schools, with reference to the effect of administering iodin. They concluded (1) that simple goitres may be prevented by the administration of small amounts of iodin; (2) simple goitres disappear or are markedly decreased by the use of a small amount of iodin given internally; (3) there is no danger of producing toxic conditions, such as Basedow's disease; (4) simple goitre is probably the easiest of all known diseases to prevent.

A TEST FOR DETERMINING "POTENTIAL HYPERTHYROIDISM." Dr. Emil Goetsch has suggested a unique procedure for determining the potential possibilities of the thyroid in the particular individual. The principle and procedure of this test are no doubt familiar to all. One-half cubic centimeter of 1 to 1000 solution adrenalin is injected subcutaneously and subsequent observations are made upon pulse-rate, blood-pressure, urinary secretion, blood sugar and objective and subjective symptoms. It has served a great purpose in our clinic, not only from a diagnostic and prognostic standpoint con-

[10] Am. Jour. Physiol., October, 1919.

[11] The Isolation in Crystalline Form of the Compound Containing Iodin Which Occurs in the Thyroid, Jour. Am. Med. Assn., 1915, lxiv, 2042.

cerning thyroid conditions, but it has increased our interest in endocrin disturbances in general.

By way of improvement in technic we would suggest that the administration of the adrenalin be preceded by a preliminary course of hypodermics of sterile water. It gives the patient time to be accustomed to the hospital, to hypodermic medication and to the routine of close observation. We find the results much more reliable when this precaution is taken. The effect of adrenalin administered in this way and for this purpose, we feel, is subject to a number of interpretations. At present we believe we can recognize two or three rather distinct groups of cases as the result of the activating injection. One is a group in which the circulatory symptoms—tachycardia, palpitation and precordial distress—predominate; another in which the nervous symptoms, such as substernal distress, *i. e.*, globus, "internal tremor," trembling of the hands, restlessness and agitation are present, with scarcely any acceleration of the pulse-rate. And a third group, in which only disturbance of the carbohydrate metabolism occurs, as evidenced by hyperglycemia and mild glycosuria as the leading factors. In the case of the first patient whose history I presented the Goetsch test was negative in so far as an increase of the circulatory and nervous disturbances was concerned, but sugar was found in the urine, and a sugar tolerance test also produced a glycosuria and a hyperglycemia. When the patient was not under the effect of adrenalin there was no hyperglycemia.

We are of the opinion that many points will have to be cleared up before the full significance of the Goetsch test will be known. May it not be possible that with the Goetsch test we might find there is a stage in the course of the hyperthyroid condition, even preceding that of appreciably increased metabolism, in which the Goetsch test might be positive, and thus warn us of what is about to take place?

Enough has been said to justify the claim that we are in possession at present of data from the laboratory which has greatly stimulated our interest and increased our ability to recognize and diagnose early endocrin disturbances. It must be concluded that the internist who is in possession of the data to which meager reference has already been made should now be in a position to recognize the first alteration of function which points to disturbance or disease of the endocrin system, and should forestall by prophylactic measures the impending disaster. In the case of the thyroid, for example, where there is evident hypertrophy, one's attention should, of course, be called at once to the possibility of early symptoms of Graves's disease; but when there is no apparent hypertrophy the slightest symptom should receive careful consideration.

It is not the purpose of this paper to go into the details of the symptomatology, such as the definite loss of weight in spite of

unimpaired appetite, the increased amount of energy discharged, the physical and mental restlessness, the tremor, the loss of vascular tone, the acceleration of the pulse-rate and the so-called internal tremor to which the thyroid patient so frequently refers. It is intended rather to call attention to very early functional changes which may be recognized by certain tests, showing an unbalanced endocrin system. If these changes are taken at their face value and early treatment instituted the results in many cases would no doubt be different. Medical treatment would be more effective and the surgeon and roentgenologist would not need to be called so frequently as they are at present. This I believe to be especially true in so far as the thyroid gland is concerned.

In a paper by Dr. John H. Musser, read in Chicago in 1911, on Problems in the Treatment of Exophthalmic Goitre,[12] he says in his conclusions: "Finally, my conviction is that the surgeon does too much and the internist too little in the treatment of goitre." This was probably the last paper Dr. Musser read. With our present knowledge we would no doubt say, in addition to what Dr. Musser has said, that the internist besides doing "too little" does it too late. Nothing will clear up the goitre problem more satisfactorily and promise better therapeutic results than prompt recognition and establishment of early, definite and earnest treatment. Under such conditions a large proportion of cases will no doubt get well with so-called medical treatment. The fact, of course, must never be lost sight of that any pathology of the thyroid gland should receive the same consideration that similar pathology does in other parts of the body, with this difference, however: The far-reaching effect of suddenly disturbing thyroid secretion must always be kept in mind. If a cyst is present, or an adenoma, or a malignant neoplasm, it should be considered along the well-established lines which such pathology receives when it occurs in other parts of the body. And on account of our lack of knowledge of the etiology of exophthalmic goitre there must be no varying from the general principles which obtain in the treatment of any disease. Particularly is this true of the chronic infections due to local foci and of the acute general infections. We could all no doubt cite instances of the apparently very close relation of thyroid disturbances to diseased tonsils, infected sinuses or abscessed teeth. Unquestionably these conditions should all be taken care of on the basis of their own pathology, whether there is thyroid disturbance or not. This means, therefore, that surgery has a large field in diseases of the endocrin system, and especially in diseases of the thyroid.

In speaking of medical treatment, on account of the peculiar individual phases which each case may represent, it is best only to mention the principles upon which it is based. It is based upon the

[12] Am. Jour. Med. Sc., cxliii, 810.

principles established by those investigators to whom reference has been made. The disturbance of function of that nervous mechanism which Cannon, Mills and others have described must be controlled. This means rest in varying degrees. It may mean, also, very active medication, such as nerve sedatives—the bromides for example. The loss in weight which Du Bois has explained must be overcome. This means abundance of food—indeed, forced feeding. The disturbance of a certain secretion to which Marine and Kimball have called attention must be balanced by careful medication. This means measures to forestall or to correct a changed secretion. No one up to this day has better outlined a course of treatment, especially in so far as rest and forced feeding is concerned, than has Dr. S. Weir Mitchell in his plan of the rest treatment. The possibilities of restoring nerve function, mental balance and loss of weight by the proper application of the principles laid down by Mitchell is recognized by all. One need only read Mitchell's little book entitled *Fat and Blood* to get a definite outline and all the details of the rest treatment. It is especially applicable in the incipient and early cases of thyroid disturbance. The rest and feeding must be prolonged until the results are obtained and securely held.

The late Dr. Janeway, in discussing a collection of papers referring to thyroid conditions and the various treatments therefor, said: "I have seen that symptoms when recognized early permit of successful medical treatment in spite of the fact that for the patients studied nowadays in hospitals surgery is usually necessary. One of the reasons for difference of opinion between surgical and medical men is that we tend more and more to treat our patients in the hospital (where they arrive late). In private patients who will early coöperate, however, the medical man may accomplish cures which are permanent. Such patients must be carefully selected and more carefully managed.[13]

This brings us to the crux of the goitre question in so far as the treatment of all cases in whatever stage is concerned. It is the proper selection of cases, or rather the proper selection of the treatment, for the particular individual patient. Unfortunately, patients do not usually consult a physician in the early stage to which attention has been called. Prophylactic treatment is not always applicable. Yet patients must be cared for at whatever stage they present themselves. Early in my medical practice I determined upon a classification of goitre patients which has been very helpful to me, and which up to the present I have not seen fit to abandon. It furnishes a rather satisfactory working basis for the determination of the proper treatment in the individual patient. It does not preclude any classification, thus far suggested, of diseases of the thyroid gland based upon demonstrable and well-recognized pathology.

[13] Janeway, T. C.: Boston Med. and Surg. Jour., 1916, clxxv, 685.

Patients having disease or disturbance of the thyroid gland are divided into four groups:

Group 1. Those patients having hyper- or hypothyroidism without any apparent pathological change in the gland. No change in the size or shape of the thyroid is demonstrable physically. These may be early cases in which later pathology will become manifest, or they may be well-advanced cases with no pathology of the glands. If one is keen in recognizing the early symptoms of thyroid disturbance this class may be large. The symptom-complex, however, is often remarkably definite if one will go after it. At other times a study of the basal metabolism and possibly the application of the before-mentioned Goetsch test may be necessary to confirm the suspicion. The treatment in these cases is definitely medical. I do not know of any attempts of treatment by roentgen ray in these cases, unless it be in those cases in which the thymus gland is enlarged. Surgery is not necessary.

Group 2. Those patients having an enlargement of the thyroid but in which from the age of the patient and the absence of certain symptoms the diagnosis of adolescent goitre may be made. It occurs in young girls about the time of the establishment of the menstrual period. It may also occur in boys at the age of puberty. The enlargement is usually temporary. There are, of course, notable exceptions. If any definite treatment is necessary it is medical. Usually time and careful prophylactic measures may prevent the hyperthyroid syndrome. The iodides in small doses or small doses of thyroid extract may be advisable. One of my cases was a notable exception: A young girl was brought to me at the age of twelve with a slightly enlarged thyroid. It had been noticed for about four years, or since she was eight years old. Advice had already been given that it was an adolescent goitre and would likely disappear in due time. There was no reason at that time for advising anything to the contrary, as there were no symptoms. The tonsils were diseased and removed without any untoward symptoms. Definite prophylactic treatment was instituted. When the periods came on at the age of fourteen there was no change in the size of the gland, but at the end of two years it was larger. No symptoms of hyperthyroidism were noticed, but the patient wished a lobectomy for cosmetic purposes if for nothing else. A partial lobectomy was done under local anesthesia. The right lobe and the isthmus were removed. It proved to be a parenchymatous hyperplasia. Within a year of the operation the remaining lobe enlarged rapidly and symptoms of hyperthyroidism were noted. A second operation was considered, but finally it was decided to apply roentgen rays. After eighteen applications by Dr. Russell H. Boggs the swelling had about disappeared. This was three years ago. The patient lost her symptoms and seemed well. She has since been in college and has done heavy work; she had an operation for

appendicitis and is living a normal life. The neck is now normal and there are no symptoms. This is undoubtedly an exceptional case, for among a large number of this group of cases this is the only one that seemed to require other than medical care. Most of these patients acquire a normal thyroid after the menstrual periods are fully established. On account of this it is extremely difficult to estimate the real value of any treatment which may be instituted.

Group 3. Those patients having an enlarged thyroid with a definite hyperthyroidism active or at times potential. The enlargement may be due to a hyperplasia of a parenchymatous type (true Graves's disease), or it may be a colloid goitre, a cyst, an adenoma or any combination of these conditions. This is a group of patients in which the course of treatment is occasionally extremely difficult to decide upon. It depends largely upon the stage of the disease or condition present at the very time the patient is seeking advice. Two principles must be kept in mind: (1) Any pathology of the thyroid should receive the same prompt consideration as similar pathology does elsewhere in the body. If the indications are for surgery it should be undertaken; if for roentgen rays the same obtains. More will be said of this when discussing group four. (2) Due regard must be given to the stage, or degree, of secretion of the thyroid gland, determined by its effect upon the general health of the patient, before deciding upon any course of treatment. In toxic goitres of extreme degree and in true exophthalmic goitres medical treatment may be the only safe treatment at first, and may be a necessary preliminary to later surgical or roentgen-ray treatment. If, after a successful course of medical treatment, the thyroid gland still presents such pathology as would ordinarily require surgical interference, surgery should be undertaken promptly, *before there is a recurrence of disturbed function.*

In certain cases the intoxication may have reached such a stage that medical treatment, *i. e.*, physical and mental rest, abundance of food, support of the circulation and nerve sedatives, however carefully prescribed, will not bring about such amelioration as to make an operation a safe procedure. Under such circumstances it may still be safe to use roentgen-ray treatment, either as a preliminary to operation or without any thought of a subsequent operation. In these cases roentgen-ray treatment has been most satisfactory. In several cases where it was begun only as a preliminary treatment the results were so satisfactory that it was continued until the symptoms subsided and the swelling practically disappeared. Of course, there are occasionally fulminating cases which run a rapid course and for which no treatment, however carefully planned, is of any avail. One such case seen some years ago was most remarkable. The patient was a child's nurse. She had charge of two children in a family. Both contracted scarlet fever and died violent deaths within a week on account of kidney

complications associated with uremic convulsions. The nurse, who was very much attached to the children, harbored the idea that she was directly responsible for bringing about the contagion. She could not be convinced to the contrary and brooded continually. She had previously been perfectly well. Her pulse became rapid, the thyroid gland enlarged, the eyes protruded and tremor developed. The diagnosis was evident. Notwithstanding every care she became delirious, later comatose and died. The whole course of the disease was run in just two weeks. It will be seen that in group 3 the success of any treatment is largely dependent upon the proper selection of cases. The problem is practically the same as it is in gastric and duodenal ulcer. There are some patients who will get well with medical treatment and remain permanently well, while there are conditions in others which will interfere with recovery until surgery is undertaken, or roentgen rays are applied, and finally there are those who will not recover with any treatment. These are the fulminating cases, or the neglected chronic cases with definite vascular or nervous disturbances.

Group 4. Those patients having definite pathology of the thyroid, enlargement without any disturbances of thyroid function. This group includes malignant tumors, such as carcinomata, also the so-called "simple" goitres, or colloid growths, as well as the adenomata and cysts, and inflammatory reactions due to tubercular, luetic or other infections. They really have no disturbance of internal secretion, but may be potential cases. These are imperatively surgical conditions, especially when malignant or when producing pressure symptoms interfering with breathing or swallowing. Certain of these conditions, such as the adenomata and colloid goitres, yield satisfactorily to roentgen-ray treatment, which under certain circumstances may be preferable, but in emergency surgery is imperative.

By following such a grouping of patients as just described I have been able to advise more definitely as to the line of procedure in disease of the thyroid gland. There are, of course, border-line cases, but this occurs in any classification.

The first group includes strictly medical cases; the second group may need nothing but prophylactic care and extremely careful medication; when they need more they are already in the third group; the third group may be medical for a time and later surgical or roentgen ray or both; the fourth group is surgical always, but may present an enticing field for roentgen-ray investigation.

The physician who has only one treatment, be it medical, surgical or roentgen ray, either sees only one class of cases or fails to recognize a large class which might be successfully treated otherwise. While I would prefer to have the surgeon and the roentgenologist settle their own differences, if there are any, on this question, as an internist I feel it my duty to express an opinion. The internist usually

sees the cases first, no difference what stage of the disease may be presented. If medical treatment is not indicated, or if medical treatment has failed, or under certain circumstances if it has succeeded, he should be immediately in touch with the surgeon or the roentgenologist, or both. If he is as familiar with his case as he should be, he will go into such a consultation with pretty definite convictions. From my own experience I would say as between surgery and roentgen ray, that the former has a far larger field of application, and in skilful hands is comparatively safe. It has the added advantage of furnishing definite information, in that the tissue removed may be studied and the nature of the pathology determined. This is of the utmost importance for the future conduct of the case. The roentgenologist is necessarily frequently not altogether sure of the condition with which he is dealing.

The results of operative treatment are sometimes immediate, so that the patient is able in a short time to return to his usual life or occupation. On the other hand, the roentgen-ray treatment presents some advantages which cannot be passed by and which appeal to one very strongly. It is comparatively without danger: it leaves no scar; it is painless and gives very little inconvenience; if it is unsuccessful, surgery may be undertaken with possibly less risk.[14]

The absolute safety of the procedure may be questioned. May it not be possible by roentgen ray to destroy the function of the gland entirely, as happens in the radiation of the ovaries, and produce a myxedema? The surgeon from the time he entered this field has been reminded of the dangers of removing too much glandular substance, and there are records of unfortunate results. What assurance has the roentgenologist that he may not have similar experiences? These are some of the questions which concern the internist especially.

In conclusion the following summary might be offered:

1. Exophthalmic goitre, or hyperthyroidism from other causes, should be recognized early and treated promptly, on lines specified.

2. The earlier it is recognized the more likely medical treatment will be sufficient and give permanent results.

3. The neglected cases, or the cases having definite pathology besides, are likely to require surgery or roentgen ray, or both. In this is included treatment with radium.

4. The roentgen-ray treatment of the enlarged thyroid presents most attractive advantages, but the indications for its use do not seem so definite yet, and the results are not so certain.

5. In hyperthyroidism the roentgenologist and the surgeon at best can only break through a vicious circle for which the internist may or may not have been responsible.

[14] Malcolm Seymour: The advantages of Roentgen-ray Treatment, Boston Med. and Surg. Jour., 1916, clxxv, 568.

HUMAN ARTERIOSCLEROSIS: SOME REMARKS CONCERNING ITS ETIOLOGY AND SYMPTOMATOLOGY.

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Etiology. Arteriosclerosis is another term for aging. It means that the vascular domain, especially the arterial portion, and also other tissue cells, are wearing out. There are some factors which we feel certain, and others which we suspect, speed up this aging process, yet in most instances we do not know the exact *modus operandi*. Among the factors which play an active part we find (1) the wear and tear of life, (2) infectious processes, (3) intoxications, (4) mechanical strain. The relative importance of these factors doubtless varies in individual cases, as does their relative importance, in the opinion of many observers who have given thought to the subject.

1. *The Wear and Tear of Life.* It is easy to grasp what is meant by this title. It is very difficult, if not impossible, in the present state of our knowledge, to accurately explain the concrete sequence of causes and events.

Our first thought, perhaps, suggests heredity. We know that certain organisms and machines are more enduring than others; more capable of adjustment to surrounding circumstances and more resistant to certain types of strain. But, unfortunately, we often cannot assign the reason, nor do we know the exact nature of the strain. The influence of heredity is quite as impossible to explain as is growth and longevity in different species of animals. Why does the swan live so much longer than the sparrow or the elephant than the mouse? Why do some individuals live to a ripe old age, having passed through hardships, physical strain, infectious disease, exogenous intoxications and severe trauma, while others succumb early and easily?

Oliver Wendell Holmes on being asked how a man should proceed in order to live to the age of seventy years, replied that he should pick his ancestors for one hundred years before he was born.

It is easy to show by mathematical formula the enormous and increasing strain to which the heart and arteries are subjected. Also that these strains may be and often are much enhanced by habits of life, such as severe muscular effort, and by causes such as chronic arterial hypertension. But, again, this leads us once more into the maze. Why the difference in individuals?

Some things, however, it appears do exercise profound effects. It is agreed that the modern high-tension life, kept under the spur

by ambition and competition, with inadequate mental relaxation and with insufficient physical exercise, which helps to redistribute blood and relieve congested vascular areas, does much to produce arteriosclerotic changes.

2. *Infectious Diseases.* It has been said, with truth, that "Venus loves the arteries." One of the definite advances of our knowledge within recent years has been the frequency with which syphilis produces disease of the aorta. It appears that although the involvement of this vessel is a frequent if not constant, as well as an early lesion, its symptoms rarely manifest themselves with obtrusiveness for sixteen years. As an illustration of this the army experience may be quoted. Out of 1,000,000 men examined 11,562 were rejected for cardiovascular diseases, and among these only 20 men were found to have aortic aneurysm; even aortic insufficiency of luetic origin was not common. With syphilis as a known, important factor of arterial disease, and with the current estimate that about 15 per cent. of our population has been thus infected, many cases of arteriosclerosis are accounted for. Other infections, such as typhoid fever and tuberculosis, may also be held accountable for some cases. In addition to the clinical evidence, aortic atheroma has been produced by the experimental injection of various pathogenic bacteria in animals. Focal infections doubtless also play a role.

3. *Intoxications.* Lead, alcohol and tobacco are regarded as potent factors. In regard to the former there can be no question. Lead may act (*a*) directly upon the bloodvessels or indirectly through the production of (*b*) nephritis and (*c*) gout. The role of alcohol is more in doubt, and difficult to evaluate, owing to the coincident presence of other causes. As an important etiological factor alcohol *per se* has certainly lost caste in recent years. Perhaps our great national experiment may in the future throw light on this subject. Tobacco establishes a far better claim as a noxious agent than alcohol. Experimentally the injection of nicotin in small quantities increases the secretion of epinephrin. Arterial lesions are readily produced by the injection of nicotin, and blood-pressure changes can easily be demonstrated in human beings. In a certain type of arteriosclerosis, thrombo-angeitis obliterans, a Jewish heredity, and the cigarette have been especially incriminated. And yet when one considers the number of heavy users of tobacco who live to old age, one wonders how great a role tobacco plays.

4. *Mechanical Factors.* Arterial hypertension, often associated with nephritis, justly receives credit for many cases of arteriosclerosis. This may be more or less localized, as in the aorta and brachial arteries of the laborer, or in the cerebral sclerosis of the man who works with his brain. As a rule, however, the process is more generalized, although the heart or the brain may be the chief point

of attack. As Osler has said, "The tragedies of life are largely arterial."

5. *Chemical Factors.* The whole trend of modern medicine is toward chemistry. Is it not natural to turn to chemistry as an explanation of our riddle?

(*a*) *Auto-Intoxication.* Metchnikoff's conception of arteriosclerosis as a result of "auto-intoxication," due to production and absorption of poisonous products, putrefactive in character and arising from the intestinal flora, has attracted much attention. While the possibility of this hypothesis in some cases cannot be denied it certainly has not been proved to be a constant or even frequent factor.

(*b*) *Internal Secretions.* Attempts have been made to show that arterial hypertension and vascular disease may result from disturbance of the internal secretions. We know that the medullary part of the adrenal gland and the infundibular portion of the pituitary are potent vasoconstrictors. Arterial lesions are readily produced experimentally by the injection of epinephrin, although they differ in type from human arteriosclerosis. Much stress has been laid upon epinephrin as a factor in the causation of arteriosclerosis, it being believed that it acts chiefly by its effect on the vasa vasorum. Contraction or occlusion of these vessels would naturally impair the nutrition and resistance of the arteries. In some clinical cases of arteriosclerosis, disease of the vasa vasorum is the only change demonstrable. Such lesions may produce both intimal and medial necrosis. (Cowan.) Degenerative disease of the adrenal glands, as seen in Addison's disease, is associated with hypotension; but this line of reasoning apparently leads us astray, since the adrenal glands are, it appears, only emergency organs which are not concerned in the normal maintenance of blood-pressure, and an increased epinephrinemia cannot be shown to exist in chronic hypertensive disease. It is possible, of course, that an individual living under continued high tension, with periods of excitement and strain, may suffer some arterial damage from this cause, but that it is much of a factor cannot be maintained.

Again, the secretion of the thyroid gland exerts a marked influence upon the circulation, greatly increasing the work of the heart, the rate of blood flow and dilating the peripheral vessels. Arterial thickening is a pronounced feature in long-standing cases, as is also cardiac hypertrophy. It has been suggested that an excessive protein diet acts through its effect upon the thyroid gland. It being pointed out that the plethoric gourmand presents many symptoms similar to those of hyperthyroidism, such as flushing, a sensation of warmth, palpitation, nervous irritability, increased blood-pressure, etc. (Sajous.) There also appears to be an interrelation between the ovaries and other glands of internal secretion. Vasomotor disturbances are common at the time of the menopause,

and arterial hypertension is often first manifested at this time. These and many other thoughts along this line are suggestive and interesting, but largely speculative and not explanatory of the basic cause of arteriosclerosis.

(*c*) *Protein Metabolism.* If then the chemistry which we speak of as endocrinology fails to solve the riddle of arteriosclerosis, can we turn to a more fruitful field, that of metabolic chemistry? In this domain we are equally at a loss for an answer. It is probable that certain products resulting from the digestion of protein or the products of metabolic activity—protein catabolism—may exercise deleterious effects upon the vascular system, but experimentally the products of hydrolysis and amine formation from protein are dilators of vascular structures. As an example, histidin, one of the common amino-acids, may be mentioned. Of course, it does not follow that only vasoconstrictors can produce arterial damage. Arterial lesions can be produced experimentally by the injection of toxins or epinephrin even if a rise of blood-pressure is prevented by the simultaneous injection of the nitrites. Clinically, it seems established that overindulgence in food, especially protein food, has deleterious results. Certainly, the withdrawal of proteins and the restriction of food generally to the point at which only the nutritive needs are supplied is often followed by a great amelioration, if not an actual disappearance, of hypertensive symptoms.

SYMPTOMATOLOGY.

Bearing in mind the fact that arteriosclerosis is a general disease affecting not only the circulatory system, but probably also other tissues as well, it is not surprising to find that its symptoms may be practically coextensive with the ailments which flesh is heir to. It is equally obvious, inasmuch as arteriosclerosis is a normal biological development, which may begin at any age, that the early manifestations may be slight, vague, ill-defined and difficult to evaluate.

Many cases diagnosticated as indigestion, biliousness, neuralgia, neurasthenia, asthma, bronchitis are in reality the early manifestations of arterial disease. It is well to be skeptical regarding what appear to be purely functional derangements without demonstrable cause in individuals past middle life. It was doubtless with this or a kindred thought in mind that the following advice was offered by an experienced practitioner: "When the patient complains of his stomach, examine the heart; when he complains of his heart, examine the stomach." It is hardly necessary to recall the number of sudden deaths attributed to "acute indigestion."

It would profit but little to enumerate *in extenso* all the different symptoms which arteriosclerosis may occasion, but a few phases may perhaps merit allusion.

As is well known, sclerosis of the arteries is nearly always general, yet in a given case certain organs or systems are the chief sufferers. It is customary, therefore, to class the cases as (1) cardiac, (2) renal, (3) cerebral, (4) peripheral, (5) abdominal, (6) nervous. In each instance symptoms may arise as a result of spasm, diminution in caliber, thrombosis or rupture of a given vessel. Such symptoms are usually but not always brought on when an extra demand for blood, either locally or in other areas of the body, exists. Thus in the cardiac type one has as subgroups those in which (*a*) myocardial, (*b*) valvular and (*c*) coronary lesions and symptoms predominate the picture. In the renal group one finds (*a*) cases associated with the contracted kidney and often with very marked secondary vascular changes resulting from toxemia and hypertension, and (*b*) those cases which show the true red, beefy sclerotic kidney and often exhibiting few if any urinary symptoms. In the cerebral type one finds not only a loss of mental elasticity, an inability to concentrate attention or to enjoy things that once made an appeal; but also psychasthenic manifestations, vagaries of conduct or outbursts of excitement in people who had previously steered a straight course and kept an even keel. One also encounterers amnesias and temporary failure, either partial or complete, of vision, hearing or consciousness; also aphasias.

The peripheral type is chiefly exemplified by vascular spasm, intermittent claudication, spontaneous cramps, neuritic pain as in erythromelalgia, localized gangrene, etc.

We must speak with less assurance regarding the abdominal type. Most often one sees flatulent indigestion simulating cholelithiasis or ulcer. The latter may actually exist as a result of localized endarteritis. A special type of angina, angina abdominis, has been described.

Finally, in the nervous group one finds vertigo and even convulsions epileptiform in character. Such convulsions occurring in individuals past middle life, in the absence of syphilis, lead and uremia, usually have an arteriosclerotic basis.

Arteriosclerosis may occur in infants, and when one takes the trouble to look for it, it is not infrequently found in young adults who may at the time show no vascular symptoms The symptoms in these cases usually do not appear until arterial hypertension becomes an added factor, and this, in many instances, may be years after the peripheral arteries first show definite thickening.

But according to the modern conception, as has already been stated, arteriosclerosis is a general disease; general, not only in its arterial distribution but also in the fact that all the tissues of the body may show the effects of the disease even independently of the disturbances which result from a diminished blood supply. In other words, the chemical changes which cause vascular disease affect other tissue cells directly, just as they do the arterial walls.

Hence much attention has been focussed upon a so-called "presclerotic" stage. Only after this stage has advanced will one be able to demonstrate arterial changes. Still later, as the case progresses, definite evidences of circulatory, renal or cerebral failure, or a terminal infection, will appear upon the scene. In the first stage various and often ill-defined phenomena make their appearance.

The earliest stage is always difficult, sometimes impossible of recognition. Generally, one notes what appear to be a beginning loss of bodily vigor, resistance to strain, or to infection, either with or without what appear to be slight functional derangements, involving the digestive, circulatory, renal or nervous systems. Sometimes the only noticeable changes are those of the skin, which becomes dry, wrinkled and atonic, with a diminished sebaceous activity, a tendency to chap, and suggests a possible hypothyroidism. Or perhaps the patient may simply show an apparently causeless anemia.

There is in the minds of many much confusion between arterial hypertension and arteriosclerosis. Indeed, the terms are unfortunately sometimes used interchangeably. Of course, the two conditions are often simultaneously present and prolonged hypertension often leads to arteriosclerosis. But that the reverse is true appears more than doubtful. (1) To begin with we are confronted with the great senile group whose arteries may be like pipe-stems but whose pressures are practically normal; (2) we have the large group of hypertensive cases in whom the increased pressure begins in middle life, is maintained at a very high level and precedes by many years the appearance of demonstrable arterial thickening; (3) it is not conceivable that a splanchnic vascular spasm can be maintained over months and years of life, especially without producing more local intra-abdominal disturbances than is the case, to say nothing of the fact that splanchnic sclerosis is but rarely demonstrable at autopsy.

In conclusion, it seems that clinical arteriosclerosis may simply be an involutional process, a part and parcel of aging; or it may be mechanical or toxic in origin. Just how this involutional process is brought about we are not in a position to state. But it seems more than likely that it will ultimately be shown to be the result of chemical changes associated with the bodily metabolism, which exert their effects upon the individual visceral, vascular and somatic cells, either directly or through the mediation of the ductless glands.

ARTERIOSCLEROSIS IN WILD ANIMALS.[1]

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THE study reported here is a part of a general scheme of the Laboratory of Comparative Pathology at the Philadelphia Zoölogical Garden to place on record a review of the lesions found among the animals at the autopsy table, thus attempting to fulfil the objects of the collection, so aptly put in a quotation from Bacon's "New Atlantis," that we have upon our walls: "We have also parks and enclosures of all sorts, of beasts and birds, which we use not only for views and rareness, but likewise for dissections and trials, that thereby we may take light what may be wrought upon the body of man." The subject of vascular disease was taken up as the first step in a study of the cardiorenal system and has led to some interesting observations. The morbid processes covered in this report include only those described in human pathology today as productive endarteritis and degenerative arteritis or arteriosclerosis; it will be called angeitis as a collective term. Among the animals domesticated by man these lesions have received scanty attention, possibly because their association with other lesions is not pronounced, but mostly because they are relatively rare. An accepted standard text-book, Hutyra and Marek, treats the subject casually, laying greater stress upon the varieties caused by parasites, while Zinserling questions whether arteriosclerosis, like that seen in the human being, ever occurs in the horse. Another author has observed it in heavily worked draught horses. Arteriosclerosis has also been seen in dogs, and Kollisch states that the essential pathology is the same. The incidence among domesticated animals, as a whole, is not available, but it must be low. However, the occurrence of angeitis among wild animals is likewise not great, for we present the result of an analysis of 5464 autopsies, among which only 86 cases were discovered, that is about 1.5 per cent. The distribution of these cases is as follows:

Mammals autopsied, 1806; angeitis, 33 or 1.8 per cent.; birds autopsied, 3571; angeitis, 53 or 1.4 per cent.; all others autopsied, 87; angeitis, 0.

Before going on with the consideration of the features of these groups and lesions, it might be well to consider for a space a few general facts concerning the similarities and differences among man, lower mammals and birds. In so far as the gross anatomy of mam-

[1] This is a preliminary report upon the subject, the first step in the larger field of cardio-vasculo-renal pathology. It was read before the College of Physicians, Philadelphia, February 4, 1920.

mals as a class is concerned there are relatively few differences, the cardiovascular structures being built upon the same general plan and the physiology being very similar. The minute structure is likewise much of the same kind, the elastic tissues being, however, rather more abundant in the lowest mammals. The physiology of birds, however, must be constructed on a somewhat different plan, because their anatomy is quite different and their habits require a mechanism to control the distribution of strain on the cardiopulmonary system. As a class birds are, per size, oversupplied with heart and vessels, especially the trident-like group of arteries at the base of the heart. This may be in the nature of a reservoir or as a part of the pressure-regulating mechanism. The heart and the origin of the three great vessels lie more free in the thorax, and they lack the support of the well-organized mediastinal tissue seen in mammalia. Great air sacs communicating with the lungs and bones, surround this central system, which must therefore require adjustment when the birds fly high and low, dive or rise. These air sacs are present also in the abdomen and pelvis. I am unaware of any studies showing the operation of this mechanism or the seat of its control, and mention is only made to show that instead of a tissue pressure of more or less stability, as in mammals, there is a variable air-pressure in Aves. The physiological circulation of the blood, while subject, of course, to anatomical variations, is really much the same as in mammals. Microscopically a difference exists in the walls of the bloodvessels, fibro-elastic tissue being more prominent than in mammals, apparently at the expense of muscle fibers; perhaps upon this may depend some of the pathological differences. Birds have a temperature considerably higher than mammals, in some genera rising as high as 112° F.; a few genera seem to be poikilothermous. There is nothing at hand to show that the cardiovascular control is otherwise than is known for the human being. The hypophysis, adrenal and thyroid, by some thought to be essential to control of the vessels, are larger on the average in animals whose habits demand severe or prolonged muscular effort. For this statement I have no measurements or weights, but it is a matter of daily observation at autopsies on cats, dogs, eagles on the one hand, and lemures, rodents and parrots on the other hand. In the bird the adrenal cortex is distributed with nervous tissue through the body, the medulla being bare as a yellowish-brown mass, lying at the upper pole of the kidney beside the sexual organ.

If to these anatomical differences between mammals and birds and the variations of habits and habitats among both classes one adds the element of captivity, it will be at once apparent there is a very great number of variables, so great that one hesitates to draw conclusions. All that can be done is to point out certain more or less obvious groups of facts, in hope that other later observations will piece them all together.

The effects of captivity, including unnatural food and the absence of the chase, are very difficult to evaluate. While every attempt is made at the Garden to approximate natural food, it is obvious that this must be incomplete and that gastro-intestinal pathology is inevitable. As a matter of fact it is the most important factor to be dealt with in zoölogical collections. The question of senility, natural and induced by captivity, has been mentioned in several connections with animal pathology, but its effect is as yet unsettled.

The division into proliferative and degenerative angeitis may be open to some objection, but as the etiology of neither condition is settled, it is fair to consider under the former those changes which carry out the picture of the thrombo-angeitis proliferans or endo-arteritis obliterans. It happens that in our study five instances were discovered affecting vessels in or near frank inflammatory processes. The animals affected with this productive process were three birds, a rodent and an elephant. In the case of two birds and the rodent the process was associated with chronic intestinal lesions, while in the elephant it was found as an endarteritis obliterans in large vessels of the lung of chronic pulmonary tuberculosis occurring in this animal.

Degenerative angeitis, arteriosclerosis, was observed in thirty-one mammals, the orders Primates, Carnivora, Marsupialia and Ungulata being represented, while Rodentia, Lemures and Chiroptera, of which we have many protocols, are missing; four of eleven orders are affected. The lesions take the form of roughened, rather opaque, intimal changes, with degenerations of the media, but there is usually missing that well-outlined, heaped-up, ulcerating, roughened intima so characteristic of late human atheroma and present to a slight extent in the Aves. One occasionally sees fatty yellow streaks in the lining, but they seem not to go on to calcification. The aorta is by far the most affected vessel, the lesions being usually present at the top of the arch and in the thoracic portion. There is one case among mammals and one in birds with the longitudinal ridging and opacity, but not the scarring, of syphilitic aortitis. Deformity is never great and aneurysms occurred only four times. Two instances of small sacculations in the aorta were found, a sort of Mönckeberg sclerosis; once also this occurred in a bird; these have not been cut to confirm the type names. Among the thirty-one cases ten show frank chronic renal disease, about equally divided between the degenerative and glomerular types. Six animals had myocarditis of fibroid nature, one, a monkey, showing distinct coronary sclerosis and concentric hypertrophy.

This type of arterial disease seems to affect a larger percentage of orders among the class Aves, twelve of seventeen being represented. Fifty-one instances of degenerative arteritis are recorded, and of these, birds of prey, parrots, ducks and geese supply twenty-seven; ostriches and storks and gallinaceous birds, however, are well represented.

The birds of prey are divided into Falconidæ (hawks, eagles) and Catharidæ (condors, vultures). The former are aggressive, the latter timid, usually getting what is left after the former have finished, although accused by some observers of preferring spoiled meat; the two groups eat the same things at the Garden. They supply 39 per cent. of the cases among the Aves and 19 per cent. of the total reported. The lesions, while most prominent in the aorta, are found also in main branches and take the form of heaped-up, irregular, yellowish-gray intimal patches over degenerative media; the superficial deformity may be marked at times, but little scarring occurs. Calcification has not been seen, but certain patches are quite like those of the human lesions.

Parrots present exceptions to the general picture in birds, for their lesions are more common in the smaller vessels and strongly resemble senile arteriosclerosis, with its medial degeneration and calcification, as seen in man. Perhaps a considerable number of our specimens have been pets for a time, thus subjected to the effects of civilization. These birds are known to be long-lived, perhaps up to a century, and the process may be a real senile arteriocapillary fibrosis.

Gallinaceous birds, chiefly grain-eaters, show insular atheroma in sharply outlined areas, as do the larger aquatic birds, storks, herons and the like. The anserine birds vary very much in the type of lesions, as indeed they do in habits and habitat, but the larger ones, like geese, show quite clearly a patchy intimal overgrowth and fatty deposit with less evident mesial change.

Renal lesions of a chronic nature were apparent in seventeen of the fifty-one birds, very uniformly distributed in percentage among the various avian orders. Nephritis in birds is not yet well enough known to determine exactly all the varieties, but the degenerative type seems more prominent, glomerular forms being, however, clear at times. Ten birds showed chronic myocarditis. Three aneurysms were found, two in geese and one in a vulture. In two of the eagle family a definite cardiac hypertrophy was noted, one in association with myocarditis and nephritis.

In only two cases of the whole eighty-six was chronic valvulitis noted, the aortic and mitral being involved, but the notes do not attempt to estimate the hypertrophy. A word might be added concerning the occurrence of fatty deposits in the intima without evidences of sclerotic change. This lesion occurs commonly in the human being, not infrequently appearing in young persons, with and without acute infectious disease and without apparent reason for chronic vascular degeneration. Such a fatty deposition is exceedingly rare in wild animals, and, when it occurs, is more patchy than in human beings. It seems to be connected with infection.

Our study tends to confirm the general opinion of the rarity of arteriosclerosis in the lower animals, but perhaps a closer study will

reveal more cases, especially since we know the groups in which it appears. It is most common in cats and dogs, bovines, predatory birds, parrots, gallinaceous and aquatic birds, and in these groups it is most definitely developed in those living on a protein diet. The lesion is very common in the orders showing the greatest number of cases of gastro-enteritis; this is especially true of parrots, aquatic birds and herbivorous and carnivorous mammals. The aorta is more affected in mammals, the disease is more distributed in birds. A rough similarity to the human aortic lesions is to be seen in the predatory birds and some of the carnivora, while the parrots exhibit degenerations in middle-sized vessels not unlike those of arterio-capillary fibrosis.

The animals most affected are those prepared by nature for severe or prolonged physical effort, such as in fight and flight. Aneurysms occur rarely, usually at points of branching and always near atheromatous plates; they are small and seem to retain part of all coats of the vessels, seldom becoming large enough to form their wall from the surrounding areolar tissue. More males than females are listed in the series, but as we have many more males on record, perhaps the difference would be less marked if the figures were closely comparable.

TWO CASES OF FIBRINOUS BRONCHITIS, WITH A REVIEW OF THE LITERATURE.

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During the past four and a half years, in which an intensive study on bronchial asthma has been made, the sputum of asthmatic patients has been carefully examined. As a result of careful examination of the sputum 2 cases of fibrinous bronchitis were noted. Although the history which the patient gives, and to a less extent the observation of the patient during an attack suggests the diagnosis, it is the finding of long, branching casts in the sputum that establishes the diagnosis of fibrinous bronchitis.

At various intervals all cases of fibrinous bronchitis, also known as plastic bronchitis and bronchitis psuedomembranosa, have been collected from the literature, but the best, most complete and most recent review of the literature and discussion of the disease was published by Bettman[1] in 1902. Previous to 1869, because of incomplete observations, it is difficult to say just how many cases of fibrinous bronchitis actually occurred in the literature, but a safe

estimation would put the total at about thirty. The interval between 1869 and 1902 covered by Bettman's paper furnishes about 50 cases; for a list of these cases reference may be made to Bettman's article.[1] From 1902 to 1920 I was able to find 31 cases in the literature: 2 of acute fibrinous bronchitis and 29 of the chronic variety. Those cases reported in the literature since Bettman's paper will be listed at the end of this paper.

That the condition is an unusual one is evidenced by the small number of cases reported in the literature; however, the condition is not rare, since the author has learned of local cases that were never reported and of 2 other cases, observed by Dr. Lawrason Brown,[2] that may yet be reported, and, furthermore, while reading the literature, the author ran across several instances in which cases were shown and demonstrated before local foreign medical societies; but since these were never published as cases they are not indexed in the literature on the subject. A more careful examination of the sputum of patients with bronchitis, asthmatic bronchitis and the like would probably result in a still greater yield of cases of fibrinous bronchitis.

Cases of fibrinous bronchitis fall naturally into three groups, namely, acute bronchitis with expectoration of branching casts, chronic bronchitis with expectoration of branching casts and cases in which branching casts were not expectorated but were found in the bronchi at autopsy. Since the chief distinction between the acute and the chronic form is the duration of the disease or the repetition of attacks in the latter, and since most acute cases become chronic because death or permanent relief rarely follows one attack, and since the symptomatology is the same in both types, this paper will discuss only the chronic type of fibrinous bronchitis.

Branching casts may be found in the sputum of diseases other than fibrinous bronchitis. Occasionally in organic heart disease, in pulmonary tuberculosis, in penumonia and frequently in cases secondary to diphtheritic inflammation of the larynx, branching casts are expectorated. Furthermore, it is not uncommon to find small casts without branchings in the sputum of asthmatic bronchitis, and rarely these are found in association with pulmonary edema and lobar pneumonia. None of these conditions, however, are considered to be fibrinous bronchitis, since the formation of casts is secondary or related to some other condition. In other words fibrinous bronchitis is idiopathic, whereas in the condition just mentioned above the formation of casts is symptomatic.

A brief analysis of the symptomatology as usually obtained from cases of fibrinous bronchitis is as follows: The usual age of onset is between the ages of thirty and sixty, with a progressive increase of incidence up to middle life and then a gradual decline. Occupation, family history and chemical irritants seem to have little or no bearing on the disease. Often there is a previous history of some

acute infectious disease, and almost invariably there is a past history of chronic bronchitis. The onset of chronic fibrinous bronchitis is usually with an exacerbation of a chronic catarrhal condition; there may be some fever. In the acute cases there is usually a preceding acute bronchitis, accompanied by considerable elevation of temperature and frequent chills. In both the acute and chronic forms there are paroxysmal attacks of dyspnea and some cough, and these generally immediately precede the expectoration of casts. The dyspnea is chiefly inspiratory in type, the cough is very hard and there is considerable cyanosis and frequently a feeling of tightness or constriction in the chest. Symptoms are temporarily relieved by the expectoration of casts, and the severity of the symptoms are greatly out of proportion to the size or number of casts which, when raised, relieve the attack. Between the raising of large casts, small and incomplete portions of casts are usually expectorated. The amount of respiratory distress would seem to be out of proportion to the degree of limited obstruction caused by the small incomplete casts unless there is a reflex obstruction involving a larger area of the bronchial tree. Hemoptysis is rare. There may be considerable loss of weight and strength.

Physical signs do not distinguish fibrinous bronchitis from ordinary bronchitis, with the exception that when the casts are *in situ* a very coarse, dry, clicking sound, probably caused by the flapping to and fro of loosened portions of casts, may be heard with both inspiration and expiration. Impairment of resonance may be elicited and all types of rales may be heard. One would expect impairment or absence of breath and voice sounds in the area of lung that is obstructed, but this is rarely the case, probably because there is not total obstruction by the casts, which usually have a lumen.

For a detailed description of the casts reference should be made to Bettman's[1] paper. In general the large casts average 10 cm. in length and show branchings down to the seventh degree. They are white in color and have a consistency of fibrin. Many branches have little intumescentia, which may be due to air bubbles or to diverticuli. A lumen may extend throughout the branches, but often the terminal branches end either as a solid plug or as a Curschmann's spiral. Usually small portions of casts are expectorated for some time after a large cast has been expelled. Microscopically the casts usually present a fibrillar, stratified ground substance containing in its meshes leukocytes. The amount of fibrin varies and there is not as much present as one would anticipate. In each case reported only one or two distinct types of bacteria have been found, so that each author has considered that the bacteria found in his particular case were the cause of the condition. On reviewing the literature, however, the bacteria found in the different cases vary so widely that one must conclude either that any type of

organism may cause the condition or that the organisms present in the casts bear no relation to the cause of the disease.

There seem to be no definite sequelæ or complications in this disease, and only rarely is there a fatal termination as a direct result.

CASE REPORT. F. W. P., white, male, aged fifty-five years, was under observation at the Peter Bent Brigham Hospital (Med. No. 22065) from September 22 to September 27, 1919.

The patient complained of cough at night. His parents died of old age and his sisters are well. There is no history of illness or death in the immediate family and no family history of constitutional diseases. The patient has been a farmer all his life and he has always lived in Massachusetts. His past history follows: He had chicken-pox, measles, mumps and whooping-cough in childhood, scarlet fever at the age of six, and six years ago for one year he had rheumatism, swelling and redness of the joints of his fingers and toes, but this did not prevent him from working. He has had a right inguinal hernia for eight years. He has been subject to occasional colds, with some expectoration. Recently he has had nasal obstruction, which was relieved by removal of polypi. He has had no cardiorespiratory, gastro-intestinal, genito-urinary or neuromuscular symptoms. There has been no loss of weight.

The patient's present illness began five months ago, following removal of nasal polypi. Ever since their removal he has had coughing spells of two or three hours' duration almost every night. He is free from these coughing spells during the daytime, and if he sleeps sitting up the cough is much less severe. The paroxysms of coughing are followed by dyspnea of a few minutes' duration. Previous to the cough there is little or no dyspnea, but during the attack both inspiration and expiration are labored. No cyanosis has been noted. At the beginning of an attack he raises frothy sputum, then it becomes slimy, and toward the end of the attack he raises twisted white or yellow strings. There is also a white, watery discharge from the nose during the paroxysm. There is no history of hemoptysis, night-sweats or loss of weight.

Physical examination reveals nothing abnormal as regards the skull, scalp, hair, face, eyes, ears, nose, gums, tongue, pharynx, larynx or neck. He is well developed, thin but not emaciated; his mouth is negative except for a slightly offensive breath, and his teeth are negative, with the exception that there are many fillings and two are missing.

The thoracic cage is small in size and the manubrium is very prominent (chicken-breasted). Chest expansion is good and equal on the two sides; rate and depth of respiration are normal. Examination of lungs reveal no abnormalities, with the exception that a few transient, low-pitched, coarse, bubbling rales are heard, after violent coughing, over the larger bronchi in front on both sides of

the sternum. Examination of the heart, bloodvessels, abdomen, genitalia, rectum, lymphatic glands, bones, skin and extremities reveals nothing abnormal. The systolic blood-pressure is 124 and the diastolic is 80.

Examination of urine, stool and blood revealed nothing abnormal; no eosinophilia. Blood-serum Wassermann reaction was negative.

Roentgen rays showed no abnormality in the sinuses, no pus pockets about the teeth, and the heart to be normal but ptotic in type. The diaphragm was within normal limits; there was diffuse peribronchial thickening throughout both chests; the right apex showed slight mottling and the left hilus showed a slightly increased density.

During the patient's stay of six days in the hospital he slept propped up in bed in order to prevent severe coughing spells. On several occasions, however, about midnight the patient had attacks of difficult breathing, lasting about an hour. Epinephrin injected subcutaneously in 0.5 c.c. doses would give moderate relief; sterile water injected subcutaneously had no effect. The patient's temperature on two occasions was 99°, otherwise it was normal; his pulse ranged from 70 to 90 and respirations varied between 20 and 25 per minute. He had no severe coughing spells while in the hospital, but every day he did raise long branching segments of casts from the smaller bronchi. About ten days previous to entrance to the hospital he had had a severe attack of cough and dyspnea, and at this time he expectorated a large cast.

Examination of the sputum revealed a rather thick, tenacious, slimy material, in which casts and plugs were suspended. The casts were 2 to 5 cm. in length, averaged from 2 to 4 mm. in diameter, had a lumen with various intumescentia and 2 to 4 branches. The plugs were solid molds of the smaller bronchi and some ended in Curschmann's spirals. No tubercle bacilli were found in the sputum; there were a large number of eosinophils present and a few Charcot-Leyden crystals.

Microscopic examination of the casts revealed a fibrillar, stratified, ground substance; the ground substance was mucus and the fibrillar structure was fibrin in the meshes, of which there were polymorphonuclear leukocytes and eosinophils. The solid plugs on section showed a matrix with strings of mucus and fibrin infiltrated with small lymphocytes and polymorphonuclear leukocytes. No tubercle bacilli or influenza bacilla were found either in the casts or in the plugs; many cocci were present.

Bacteriological examination of the sputum alone revealed hemolytic streptococcus subacidus and non-hemolytic streptococcus ignavus; from the casts alone hemolytic streptococcus subacidus and non-hemolytic streptococcus salivarius were recovered. In obtaining these types of bacteria a portion of the sputum was washed and shaken in dextrose bouillon, and then blood-agar plates were poured;

the casts were teased out, washed in sterile saline, shaken and macerated in dextrose bouillon from which blood-agar plates were poured. Smears of the macerated casts and plugs revealed no tubercle bacilli and no influenza bacilli; only cocci in chains were seen.

The second case will not be given in detail, since it has already been published by Dr. Henry A. Christian[3] in the *Medical Clinics of North America*, Boston number, 1919, II, 1255. A summary of this case follows:

D. R., white, male, aged twenty-two years, a plumber's helper by occupation, entered the Peter Bent Brigham Hospital (Medical No. 9990) complaining of breathlessness. His family history, past history, and habits are unimportant. There is no history of exposure to irritating fumes.

The present illness began suddenly three months ago in September, 1918. He was awakened by a severe cough, a feeling of breathlessness and oppression. After an hour the attack gradually passed and he went to sleep. Each night since he has had similar attacks which have increased in frequency, duration and severity. Cough always precedes the attack and the raising of thick, stringy sputum relieves the attack. During the attack expiration is easy, but inspiration is difficult; there is considerable wheezing and cyanosis and a feeling of tightness in his chest. During the day he has mild attacks directly after eating. Epinephrin relieves the attacks. In November, 1919, two months after the first attack, many polypi were removed from his nose without apparent benefit. He has lost forty pounds in weight.

Physical examination is negative, with the exception that examination of the lungs reveals a slightly hyperresonant note throughout; expiration is distinctly prolonged and slightly high pitched and a few scattered crepitant rales are heard throughout the lungs.

Roentgen rays showed that the entire right chest was less radiant than the left and a diffuse peribronchial thickening which is more marked on the right side and dense glands at both lung roots.

The patient was under observation twenty-four days. During this time his temperature usually varied between normal and 99°, with an occasional swing to 100°; his pulse varied between 80 and 100 and his respirations were usually 20 per minute, with an occasional increase to 30 per minute. Every night he had an attack of coughing, dyspnea, chiefly inspiratory, wheezing and expectoration of branching casts. Mild attacks occurred during the day. Epinephrin relieved the attacks. Administration of potassium iodide and an autogenous sputum vaccine seemed to be of no benefit. His blood constantly showed a slight polymorphonuclear leukocytosis.

Repeated examination of the sputum revealed many branching casts, many eosinophils and Gram-positive cocci in chains. No tubercle bacilli were found. A hemolytic and a non-hemolytic

streptococcus in about equal numbers were obtained by plating the sputum in blood agar. Sections of the casts revealed chiefly mucus, with a fibrin reticulum in the meshes of which there were large numbers of mononuclear eosinophils and streptococci.

Discussion of the Etiology of Fibrinous Bronchitis. The etiology of this disease is obscure. In a few cases at postmortem there was a break in the continuity of the bronchial epithelium, in others the bronchial epithelium has contained a large number of mucus-secreting cells which would suggest an exaggerated secretion from the normal mucus glands. The fact that the casts are composed in greater part of mucus would substantiate the increased secretion of mucus and the small amount of fibrin in the casts might come from the rupture or break in the bronchial epithelium. Retention of this mucus and fibrin in the bronchial tree for some time would permit of coagulation or hardening of these substances so that a cast is formed. There would be some irritation causing the accumulation of leukocytes, and since bacteria are normally present in the bronchi, leukocytes and bacteria would naturally be present in the casts.

Since in some cases of fibrinous bronchitis there is an element of neurosis, this condition has been considered by some as allied to mucous colitis. These two conditions are similar in that the intestinal casts of mucous colitis resemble closely the bronchial casts of fibrinous bronchitis, and the etiology of both conditions is obscure.

The author prefers to correlate fibrinous bronchitis with asthmatic bronchitis, bronchiectasis and chronic bronchitis. In almost all of the cases of fibrinous bronchitis, asthmatic bronchitis and bronchiectasis there is a preceding history of bronchitis, and throughout the course of these diseases there is a background of bronchitis. When patients with bronchitis develop paroxysms of dyspnea and suffocation the condition is then called asthma; in order to distinguish this condition from true bronchial asthma the author calls this condition asthmatic bronchitis. For the author's differentiation between true bronchial asthma and atypical or asthmatic bronchitis one may refer to the *Oxford Medicine* by Christian and MacKenzie.[4] If in cases of bronchitis, breaks in the bronchial epithelium, with more or less loss of it occur, fibrinous bronchitis may result; if these breaks invade the deeper structure of the bronchial tubes, thereby causing a weakening of the structure, bronchiectasis may result. In asthmatic bronchitis there is a simple catarrhal desquamation of the bronchial mucus membranes much in excess of that which occurs in bronchitis, and in fibrinous bronchitis there is a permanent loss of the epithelium. Furthermore, in asthmatic bronchitis it is not uncommon to find non-branching casts and plugs in the sputum. Very likely all of these conditions are caused by bacteria, and we know that a large proportion of the cases of bronchitis and asthmatic

bronchitis are due to bacteria, since autogenous sputum vaccines frequently relieve the condition; in fibrinous bronchitis and bronchiectasis, however, vaccines do not benefit, because too much destruction of tissue has taken place. Local lack of vitality probably explains why bacteria produce these conditions in some individuals. Because of the local lack of vitality or inadequate resistance of the bronchi to infection in some persons, bacteria, which in others are non-pathogenic, are able to set up infectious processes. Flurin[5] speaks of the "syndrome de débilité bronchique," which is characterized by hyperesthesia of the mucosa, unstable local circulation and special secretory response to any causes liable to stimulate secretion in the mucous glands.

Conclusions. Cases of fibrinous bronchitis would probably not be as rare as the literature would indicate if the sputa of patients were more carefully examined.

The diagnosis of fibrinous bronchitis is made only by the finding of long, branching bronchial casts in the sputum of cases that do not have tuberculosis, diphtheria, pneumonia or some other primary bronchial disease.

Fibrinous bronchitis is an idiopathic disease, the cause of which is unknown. Although it may be due to a neurosis it seems more closely allied to bronchitis, bronchiectasis and asthmatic bronchitis.

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CURVES OF SUGAR AND UREA AFTER STANDARD PROTEIN MEALS.

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One of the writers[1] previously reported observations of the effects of diet on the blood sugar of normal persons and diabetics. The results showed no demonstrable influence of protein in the type of cases studied. Rolly and Oppermann[2] observed a rise of blood sugar after protein meals in some diabetics. Strouse, Stein and Wisely[3] found no evidence of a rise of blood sugar in normal persons after carbohydrate-free meals. In animals with suitably severe diabetes controlled by undernutrition, Allen[4] has regularly found marked hyperglycemic curves following protein ingestion. Mosenthal, Clausen and Hiller[5] found that carbohydrate-free meals cause no hyperglycemia in non-diabetics or in some diabetics, but in other diabetics they produce more or less rise of blood sugar. This rise was found particularly in cases with initially low blood sugars, and was commonly missed in cases with marked hyperglycemia at the outset. The rise of blood urea after protein ingestion in rela-

[1] Jacobsen, A. Th. B.: Biochem. Ztschr., 1913, lvi, 471–494.
[2] Biochem. Ztschr., xlix, 1913, 278–292.
[3] Bull. Johns Hopkins Hospital, xxvi, 1915, 211–215.
[4] Am. Jour. Med. Sc., 1917, p. 153, Chart VIII.
[5] Arch. Int. Med., xxi, 1918, 93–108.

TABLE I.—50 GM. PROTEIN TEST IN FIVE NORMAL PERSONS.

	1 Mr. H. E., 22 years.				2 Dr. S., 29 years.				3 Dr. J., 34 years.			4 Miss M., 28 years.	5 Mr. C., 22 years.		
	Blood.		Urine.		Blood.		Urine.		Blood urea, mgm. per 100 c.c.	Urine.		Blood urea, mgm. per 100 c.c.	Blood urea, mgm. per 100 c.c.	Urine.	
	Plasma sugar, per cent.	Urea, mgm. per 100 c.c.	Urea, per cent.	Urea, gm.	Plasma sugar, per cent.	Urea, mgm. per 100 c.c.	Urea, per cent.	Urea, gm.		Urea, per cent.	Urea, gm.			Urea, per cent.	Urea, gm.
Before	0.106	20.0	2.63	..	0.110	13.5	1.71	..	24.2	2.42	..	15.0	46.4	2.39	
2 hours . . .	0.100	21.9	1.81	1.46	0.125	18.3	1.30	1.69	..	2.13	2.13	20.5	42.1		
4 hours . . .	0.114	28.0	2.16	1.49	0.115	19.4	1.39	2.26	28.0	2.29	2.68	..	44.2	2.74	6.44
6 hours . . .	0.105	28.0	2.38	1.45	0.115	22.6	0.64	2.18	32.6	1.75	1.96	31.4	46.4		
8 hours . . .	..	26.0	..	..	..	17.2	0.56	1.81	28.4	1.82	1.86	..	46.4	3.83	6.05
24 hours . . .	..	18.0	1.02	10.62	..	20.5	1.14	6.65	22.2	1.25	10.00	17.2	38.8	2.80	13.55
Urea excreted in 24 hours (gms.)	..	..	..	15.04	..	..	..	14.16	..	..	18.65	..	..	..	26.05

tion either to retention or metabolic variations has been investigated, especially by Addis and Watanabe.[6] An investigation was therefore undertaken to determine the curve of plasma sugar in normal, diabetic and nephritic individuals after standard protein meals and was extended to cover the urea of blood and urine.

METHODS. The standard procedure was that the subjects voided urine and were bled, then ate a breakfast consisting solely of 50 gm. protein in the form of beefsteak, and 200 c.c. water. Two patients in the series received only 40 gm. protein. Every two hours thereafter urine was passed and blood taken and 200 c.c. water drunk. After eight hours a very light supper was taken of cornstarch and candy with a trifle of fruit, having negligible protein content. Water was then taken at will, but no other food until after the blood and urine samples the next morning, which closed the twenty-four-hour period. Sugar was determined according to Benedict, urea by the urease method of Van Slyke and Cullen and total nitrogen by the usual Kjeldahl method. Blood sugars were determined in two of the normal individuals, in confirmation of the writer's previous work regarding the negative effect of protein. The sugar changes were within the limits of accidental fluctuation.

There was a very appreciable rise of the blood urea during the eight-hour experimental period, followed by a fall at the end of the twenty-four hours in every individual except No. 5. This person was a technician in the laboratory. His urine, like that of all the others in this group, was free from albumin and casts. He was supposedly in perfect health, though subject to occasional headaches. It was learned that he had by chance eaten excessive quantities of meat on the day before the test. These facts explain the exceptionally high excretion and the lower blood urea after twenty-four hours. In a strict sense this person probably has a slight nephritis, and he has been advised to follow a fairly low protein diet. Irrespective of this question it is evident that the initial percentage of blood urea is not a safe criterion of the tendency to rise after a certain protein intake.

TABLE II.—PROTEIN TESTS IN SEVEN DIABETICS.

1.—28 years.

	(40 gm. protein.) Blood.		
	Urea, mgm. per 100 c.c.	Plasma sugar, per cent.	Chlorides, mgm. per 100 c.c.
Before	20.0	0.139	568
1 hour	24.0	0.174	518
2 hours	26.0	0.174	576
4 hours	32.2	0.158	576
6 hours	36.2	0.165	587
9 hours	35.2	0.123	572
24 hours	29.0	0.122	

Excreted 11.6 grams total nitrogen.

[6] Arch. Int. Med., 1917, xix, 507–517.

2.—27 years.

(40 gm. protein.)

	Blood.			Urine.		
	Urea, mgm. per 100 c.c.	Plasma sugar, per cent.	Chlorides, mgm. per 100 c.c.	Vol., c.c.	Sugar.	Acetone.
Before	47.2	0.043	526	..	0	0
1 hour	53.4	0.070	557			
2 hours	60.4	0.068	504	85	0	0
4 hours	74.6	0.064	527	290	0	0
6 hours	76.6	0.050	546	240	0	0
9 hours	58.4	0.043	521	290	0	0
24 hours	54.4	0.040	..	1700	0	0

Excreted 14.2 grams total nitrogen.

3.—35 years.

	Blood.			Urine.		
	Urea, mgm. per 100 c.c.	Plasma sugar, per cent.	Chlorides, mgm. per 100 c.c.	Vol., c.c.	Sugar.	Acetone.
Before	..	0.074	587			
1 hour	40.0	0.110	584	260	0	0
3 hours	42.0	0.144	590	145	0	Slight
5 hours	..	0.139	555	115	0	Mod.
7 hours	44.0	0.136	590	125	0	Faint
9 hours	56.0	0.091	587	130	0	0
24 hours	50.4	0.048	561			

4.—64 years.

	Blood.	
	Plasma sugar, per cent.	Urea, mgm. per 100 c.c.
Before	0.176	24.0
2 hours	0.197	26.0
4 hours	0.205	30.0
6 hours	0.205	34.2
24 hours	0.242	39.2

5.—43 years.

	Plasma sugar, per cent.
Before	0.130
5 minutes after	0.130
1 hour after	0.144
2 hours	0.181
3½ hours	0.192
4½ hours	0.208
5½ hours	0.203
6 hours	0.203

6.—31 years.

	Blood.			Urine.				
	Urea mgm. per 100 c.c.	Plasma sugar per cent.	CO_2 vol. per cent.	Vol. c.c.	Urea per cent.	Urea gm.	Sugar.	Acetone.
Before	31.4	0.091	61.4	..	1.79	..	0	0
2 hours	35.8	0.135	68.1	87	2.23	1.96	0	0
4 hours	46.4	0.147	62.5	113	2.24	2.55	0	0
6 hours	46.4	0.132	57.8	103	2.80	2.89	0	0
8 hours	46.4	0.125	70.0	100	—	—	—	—
24 hours	34.6	0.150	—	1020	1.49	15.21	0	0

Excreted 22.6 grams urea and 14.5 grams total nitrogen.

7.—27 years.

	October 26.									November 20.						
	Blood.				Urine.					Blood.		Urine.				
	Urea, mgm. per 100 c.c.	Plasma sugar, per cent.	Chlorides, mgm. per 100 c.c.	CO_2 vol., per cent.	Vol., c.c.	Urea, per cent.	Urea, gm.	Sugar, per cent.	Nitroprusside.	Urea mgm. per 100 c.c.	Plasma sugar, per cent.	Vol., c.c.	Urea, per cent.	Urea, gm.	Sugar, per cent.	Nitroprusside.
Before .	14.8	0.314	582	51.0	..	1.38	..	4.8	Heavy	11.8	0.194	—	0.46	..	0	0
2 hours .	17.8	0.341	566	45.3	185	1.23	2.27	5.5	"	14.0	0.191					
4 hours .	18.8	0.341	558	40.4	200	1.01	2.02	5.5	"	20.5	0.272	258	1.02	2.64	0	0
6 hours .	16.6	0.319	566	43.3	248	1.36	3.36	3.66	"	24.7						
8 hours .	17.8	0.280	574	..	225	1.23	2.76	2.0	"	21.6	..	190	1.78	3.39	0	0
24 hours .	9.0	—	—	47.1	1780	0.59	10.50	0.65	"	20.5	0.269	—	0.87	..	0	0

Excreted 20.9 gm. urea.

(Total excretion lost.)

The diabetics were mostly young, but were all alike in having the severe form of the disorder, more or less completely under control by undernutrition treatment. There was a history of three to ten years' duration and an advanced degree of emaciation and weakness in all except No. 1, who had apparently been diabetic less than six months and was only slightly thin. The preceding diets ranged from fasting, in the case of the first test on patient No. 7, up to 60 gm. protein, 20 gm. carbohydrate and 1000 calories in patient No. 3. All were free from albuminuria or casts except No. 2. There was moderate edema in No. 2 and slight in No. 6 at the time of the test. Patient No. 3 had formerly been subject to edema, but was free at this time. The others had never exhibited edema. The plasma chlorides remained within normal limits in all determinations. The blood-pressure was normal or subnormal in all.

The general program of the tests was the same as above described, except that after the initial period of eight or nine hours a supper of negligible food value was given, consisting of bran biscuits, agar jelly, one dish of thrice-cooked vegetable, and coffee or infusion of cocoa shells. Certain points concerning the results in individual patients may be noted as follows:

Patient No. 1, starting with a normal blood urea of 20 mgm. per 100 c.c., showed a greater rise than any of the normal subjects, viz., to 36.2 mgm. at the sixth hour. The plasma sugar, starting with a slight hyperglycemia of 0.139 per cent., jumped to its maximum of 0.174 per cent. in one hour, and in general fell after the second hour. Undernutrition on this day is indicated by the plasma sugar, lower after twenty-four hours than at the outset, and by the excretion of nitrogen exceeding the intake. This absence of retention is of interest in connection with the prolonged rise of blood urea.

Patient No. 2 was admitted with a history not only of the severest type of diabetes but also of several mild attacks of renal colic followed by passage of small calculi, with blood in the urine at these times and pus afterward. In the hospital the albumin in his urine frequently gave Esbach readings as high as 1.5; the sediment showed enormous numbers of pus cells but no casts. Later attacks caused his blood urea to rise above 130 mgm. per 100 c.c., and at the time of the test he may be considered as representing a combination of diabetes and nephritis. Starting at 47.2 mgm. per 100 c.c., the blood urea rose to its maximum of 76.6 mgm. at the sixth hour. At the same time the twenty-four-hour nitrogen output was nearly double the intake, in correspondence with the very low diet in a patient possessing a minimum of body fat. In the days preceding the test, the rather rapid fall of the formerly intractable blood sugar to a subnormal level was another indication of danger. Under these circumstances, though the diabetes was the most desperately severe of the series, the rise of the plasma sugar from the ingestion

of protein was considerable in proportion to the original amount but trivial in absolute figures. The patient is still alive after nine months, free from glycosuria and acidosis and much improved in strength, and at home with normal plasma sugar.

Patient No. 3, with a somewhat less degree of diabetes and undernutrition, started with plasma sugar of 0.074 per cent., and reached the maximum of 0.144 per cent. in three hours after eating. Thereafter the curve progressively fell. The urea analysis before eating was lost. From 40 mgm. per 100 c.c. one hour after eating, it rose to 56 mgm. at the ninth hour. The lack of parallelism with the sugar curve is especially noticeable. During digestion a well-marked acetone reaction developed in the urine and later disappeared, due either to the protein or to the trifle of fat in the lean meat.

Patient No. 4 was tested when the diabetes was only partially under control, as indicated by the hyperglycemia of 0.176 per cent. This rose to its maximum of 0.205 per cent. at the fourth and sixth hours after eating and traces of sugar were excreted. The urea curve was parallel, starting at 24 mgm. per 100 c.c. and reaching 34.2 mgm. at the sixth hour. The morning figures of 0.242 per cent. plasma sugar and 39.2 mgm. urea proved that the patient broke diet in the evening.

Patient No. 5 had an unusually intractable diabetes for his age, and the question arose whether his slow progress was due to breaking diet or whether his hyperglycemia could actually be due to the small quantities of prescribed food. He was accordingly given the 50 gm. protein test while under constant observation in the laboratory, and the blood followed for sugar alone for six hours. The marked hyperglycemia demonstrated the true severity of the condition, and subsequent acquaintance with the patient and the ultimate favorable outcome confirmed his fidelity.

Patient No. 6 underwent fasting immediately upon admission and was given the test with 50 gm. protein as soon as the plasma sugar became normal. The plasma sugar rose to a maximum of 0.147 per cent. at the fourth hour, but was still 0.15 per cent. the next morning, indicating that the patient could not yet tolerate this quantity of protein without hyperglycemia. For this reason the protein ration for the ensuing days was set at 30 gm. During digestion the CO_2 capacity of the plasma showed some of the familiar digestive variations. The blood urea rose from 31.4 mgm. per 100 c.c. to 46.4 mgm. at the fourth hour and held this maximum for at least four hours. The two-hour urinalyses showed no retention as compared with normal persons in Table I and the total twenty-four-hour excretion was excessive, as is natural for the emaciated organism under these conditions. No acetonuria appeared during the test.

Patient No. 7 was subjected to two tests, the first during active

glycosuria before treatment, the second during the early stage of treatment, when there was hyperglycemia but no glycosuria.

In the first test on October 26 the variations in blood urea and sugar were slight and parallel for the first eight hours. This test represented a partial fast following abruptly upon the former mixed diet; therefore the result at the end of eight hours was a slight fall in blood sugar. The blood urea, on the contrary, was a trifle higher than at the first, but after twenty-four hours had fallen to the markedly low level of 9 mgm. The urea excretion was high, both for the twenty-four-hour and for the two-hour periods. The plasma bicarbonate fell distinctly during this protein test and the urinary nitroprusside reaction remained heavy. At the same time the urinary sugar fell.

By November 20 the patient had reached a point where sugar and nitroprusside reactions were constantly negative in the urine and the plasma bicarbonate normal, but hyperglycemia persisted. The blood urea started at 11.8 mgm. per 100 c.c., reached a maximum of 24.7 mgm. at the sixth hour and was still up to 20.5 mg. the next morning. The plasma sugar was 0.194 per cent. before eating, practically the same two hours after, but at the fourth hour was found to be 0.272 per cent. and was still 0.269 per cent. the next morning. The reason for the elevation of both urea and sugar here after 50 gm. protein probably is that the preceding diet had contained only 30 gm. protein. The quantitative twenty-four-hour urine collection was spoiled by the patient's fault. Though this patient's phenolsulphonephthalein test had shown an elimination of 60 per cent. the first hour and 20 per cent. the second hour, and both the urea and chloride functions had likewise been found normal, the impermeability for sugar is indicated by the absence of glycosuria with the high plasma sugars mentioned.

The first three patients listed had typical hypertensive nephritis of severe grade, with only traces of albumin and rare casts. No. 1 had slight edema and ascites, due to myocarditis and cirrhosis of the liver. Nos. 2 and 3 were free from edema. Case No. 4 was of the "parenchymatous" type, with normal or subnormal blood-pressures, extremely heavy albumin and much edema. All had been for some time preceding on diets liberal in calories but containing only 30 or 40 gm. protein. The program of the test days was as described for normal subjects. The liberal supply of water of these days was a sharp departure from the usual regimen of these patients, who had been on diets poor in both salt and fluid, and instead of sweeping out nitrogen it may have contributed to its retention.

All the tests were characterized by marked deficiency of the urea output as compared with normals, and especially in Case 1 this apparent retention was extreme. In all except Case 4 the urine volume indicated also a marked retention of fluid. The blood urea rose in all during the first eight hours, but this rise was nothing

TABLE III.—50 GM. PROTEIN TEST IN FOUR NEPHRITICS.

	1.—42 years.								2.—40 years.						3.—45 years.				4.—19 years.			
	Blood.			Urine.			Chlorides per cent.	Chlorides gm.	Blood.			Urine.			Blood	Urine.			Blood.	Urine.		
	Urea mgm. per 100 c.c.	Plasma sugar per cent.	Chlorides mgm. per 100 c.c.	Vol. c.c.	Urea per cent.	Urea gm.			Urea mgm. per 100 c.c.	Plasma sugar per cent.	Chlorides mgm. per 100 c.c.	Vol. c.c.	Urea per cent.	Urea gm.	Urea mgm. per 100 c.c.	Vol. c.c.	Urea per cent.	Urea gm.	Urea mgm. per 100 c.c.	Vol. c.c.	Urea per cent.	Urea gm.
Before	16.0	0.108	508	..	0.49	..	0.19	..	24.6	0.146	585	..	..	..	31.5	..	0.71	..	10.8			
2 hrs.	19.0	0.133	498	21.5	0.24	0.05	0.05	0.01	26.0	0.158	585	..	..	..	40.6	34	1.07	0.36	12.9	35	0.83	2.92
4 hrs.	28.0	0.143	498	..	..	..	..	..	33.6	0.144	543	51	1.82	0.93	32.3	73	1.04	0.76	16.2	105	1.79	1.88
6 hrs.	34.6	0.132	480	57.0	0.54	0.31	0.04	0.02	40.0	0.136	620	..	..	..	35.7	62	1.03	0.64	16.2	125	1.49	1.86
8 hrs.	36.2	0.106	444	36.0	0.69	0.24	0.10	0.02	37.8	0.139	593	173	1.99	2.25	34.3	25	1.35	0.33	20.5	65	1.69	1.10
12 hrs.	30.1	..	462																			
24 hrs.	27.0	..	523	750	0.25	1.90	0.27	2.02	..	..	..	275	1.47	4.04	34.3	660	0.61	4.04	10.8	1410	0.47	6.64
Urea excreted in 24 hrs. gm.						2.46								7.23				6.15				11.79

extraordinary as compared with the records of the normals and diabetics and failed totally to correspond to the comparative nitrogen elimination. In Case 1 the blood urea remained elevated at the end of twenty-four hours, as if indicating the nitrogen retention, but in Case 4 it ended at the same level where it began, and in Case 3 the elevation was trivial. Dilution probably played some part in maintaining the percentages at such levels; also, with the ample carbohydrate and calories of the usual diets, true storage as protein may have been a factor; but obviously much is unknown concerning the nitrogen retention of nephritis.

Patient No. 1 started with a normal plasma sugar of 0.108 per cent., which was moderately increased during the first six hours after eating. Patient No. 2 started with hyperglycemia of 0.146 per cent., which rose to 0.158 per cent. at the second hour, then gradually fell. Several previous writers have called attention to hyperglycemia in occasional cases of nephritis, especially with hypertension, and as such reports have been based on various methods of analysis, it is evident that the excess material present affects copper salts as well as picric acid, and may be glucose. But in view of the possible errors due to creatinin or similar substances it was deemed best to defer any conclusions concerning nephritic blood sugars until truer figures should be available by the use of the procedure recently proposed by Benedict[7] for removal of the interfering material.[8] One of us (J.) proposes to carry out further tests comparing the Benedict method with a copper reduction test for the blood sugar.

CONCLUSIONS. 1. After a standard meal of 50 gm. protein there is generally a rising curve of urea in the blood, which, as a rule, is higher in patients with severe diabetes or nephritis than in normal persons.

2. The blood-urea level is not a reliable index of nitrogen retention. In some instances, for example in diabetics, it may possibly bear some relation to the rate of protein catabolism. On the whole, it seems to be governed by so many factors of the previous diet, fluid retention and unknown metabolic conditions that by itself it forms an uncertain basis for conclusions.

3. The plasma sugar of normal persons is not appreciably altered by this quantity of protein.

4. The substances in nephritic blood, which react like sugar to the Benedict test, are increased after a protein meal.

5. A typical curve of hyperglycemia follows the ingestion of protein in suitably severe cases of diabetes. This is likely to be missed

[7] Benedict, S. R.: Paper read before the Biochemical Society, Cincinnati, Ohio, December 30, 1919.

[8] Subsequent analyses in this clinic with charcoal kindly provided by Dr. Benedict have shown no more than slight changes in the above curves. Therefore either the rise of plasma sugar after protein meals is not specific to diabetes or a diabetic tendency is thus demonstrable in some cases of nephritis.

if active symptoms of glycosuria or hyperglycemia are present, as the effect of 50 gm. protein could scarcely be expected to be noticeable amid such a surplus of sugar. Rarely also the rise may be slight in extreme exhaustion. Under the conditions of strict diet treatment this reaction to a standard protein meal may be used as a measure of the severity of diabetes and a guide both to the protein allowance and the total ration, and it has lately been used for these purposes in this clinic.

TREATMENT OF SURGICAL SHOCK IN THE ZONE OF THE ADVANCE.[1]

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The nature and treatment of shock has, in recent years, attracted considerable attention from the profession, especially on the part of the surgeon. War-time conditions naturally brought under observation greatly increased numbers of shock cases. The situation presented exceptional opportunities for the study of shock and it also demanded a plan for specialized treatment. This was all the more necessary when it became evident that in the advance zones the surgeons, when busy, were very busy, and had no time for carrying out specialized treatment. Internists, assisted and trained by physiologists, were therefore called in to help in what has generally been considered a strictly surgical problem. The plan devised by the medical department of the A. E. F. was to send into the advanced areas so-called "shock" teams, composed of medical officers (internists), nurses and corpsmen, especially trained and equipped for the treatment of shock. In preparation for the work the medical officers were given a special course in the nature and treatment of shock at the central medical laboratory at Dijon, under the supervision of Lieut.-Col. Walter B. Cannon, M.C., Boston, Mass.

In general the substance of the lectures and demonstrations given at Dijon may be summarized as follows:

I. Theoretical. Whether shock be due to hemorrhage, exposure to cold and wet, lack of food and drink, injury to muscle or nerve tissues, singly or in combination, it was agreed that in shock we find a condition of persistent low arterial blood-pressure, rapid pulse, pallor or slight cyanosis, sweating and rapid respiration, slight or

[1] The cases reported were observed by Shock Team No. 116, in charge of Captain George Strode, M.C. (Harrisburg, Pa.), and Shock Team No. 154, in charge of Captain W. R. Ohler, M.C., during the St. Mihiel and Argonne Meuse offensives. I wish to express my appreciation to Dr. Strode for permitting me to group all the cases together.

moderate acidosis. Owing to the conditions under which shock teams would have to work, blood-pressure determination was considered the best single method of determining the existence and the severity of shock. A systolic pressure of 100 was set as the minimum reading and members of shock teams were urged not to send a patient to the operating room with a pressure below 100 unless absolutely necessary.

II. Outline of Treatment. (*a*) Control restlessness by using morphin in comparatively large doses.

(*b*) Restore body heat by promptly warming the patient. The following methods were suggested and were found efficacious:

1. Hot-water Bottles (the army canteen makes an excellent hot-water bottle when the ordinary rubber one cannot be secured) placed between the feet, between the thighs, on the chest (hands folded over bottle) and in the axilla.

2. The Use of Hot Air. An efficient method in a field hospital is to place the litters on saw-horses, place one or two ordinary lanterns on the ground near the litter and close in the space by means of blankets draped from the litter to the ground. In an evacuation hospital other methods are generally available. We were able to secure small oil stoves and by means of ordinary stove pipe direct the warm air under a bed cradle covered with a blanket.

(*c*) Restore Body Fluids. 1. Force Fluids by Mouth: Hot soups, tea, coffee during first few hours. Warm soda bicarbonate drinks suggested in order to aid in overcoming condition of acidosis.

2. Fluids by Rectum. Especially indicated in severe shock or when the patient cannot take large amounts of fluid by mouth.

3. Intravenous Gum-salt Solution. In many cases of hemorrhage the infusion of certain fluids will restore the fluid bulk, and such a restoration of blood volume may be all that is needed to pull the patient through a critical period. Indications for giving gum salt are therefore the same as for giving intravenous normal saline solution. Gum-salt solution, so-called, is a 6 per cent. solution of gum acacia in normal saline. Theoretically it does not diffuse out of the vessels as rapidly as normal saline solution, and consequently gives a more lasting rise in blood-pressure.

4. Blood Transfusion. When considerable blood has been lost the reserve supply of body fluid may be so small that the tissues can give up very little fluid to the circulation. Moreover, in such instances, supplying additional oxygen as well as additional fluid is indicated. Blood transfusion presents the only means of increasing the oxygen-carrying elements of the blood.

The citrate method was adopted throughout the A. E. F. as being the most practicable of all methods. From 500 to 700 c.c. of blood was withdrawn from an arm vein of a donor directly into a bottle containing 2.1 grams sodium citrate in 100 c.c. normal saline. By taking care to have the stream of blood flowing freely and to keep

the receiving flasks rotating no coagulation resulted. The citrated blood was introduced through an arm vein of the recipient, pressure being exerted by using the bulb of a blood-pressure apparatus and forcing air into the flask. In cases of extreme shock when the blood-pressure was very low it often was necessary to cut down on the vein of the recipient. Type sera of Groups II and III were provided. Blood grouping was done according to the macroscopic method described by Vincent.[2] Members of shock teams were advised to keep a number of Group IV donors (so-called universal donors) on hand because of the saving of time in using only this particular group.

Approximately 125 cases of shock were observed during our service. In addition about 100 patients (postoperative cases) were sent to the shock ward who did not prove to be cases of shock, inasmuch as all had an entrance blood-pressure of 100 or more. It was the habit of members of surgical teams to send postoperative cases requiring special attention into the shock ward because such attention could not be given in the cold, busy, crowded general wards. It is quite possible that many of these cases were thus prevented from "going into shock." At any rate it was our feeling that the care of this type of case alone justified the work of a shock team.

In a study of the cases of actual shock an attempt has been made to group the cases according to the type of treatment as well as the severity of shock. Routine treatment consisted in rest, warmth, forced fluids (mouth and rectum), special treatment in intravenous gum-salt solution and blood transfusion. The severity of shock was determined by history, clinical appearance and blood-pressure readings. It was practically impossible to depend to any great extent upon history for determining the duration of shock Wounded men very often could not tell just when they had been injured nor how long a time it took them to reach the evacuation hospital. The loss of all sense of time on the part of soldiers who took part in the terrible Argonne fighting was, in many instances, quite amazing. Moreover, there was no time to take a detailed history. It was our business to get the patients ready for operation just as quickly as possible. Only thus could infection be controlled and lives saved.

The fear of infection, therefore, as well as the degree of shock influenced us in the treatment. Thus many cases undoubtedly were given special treatment, when, had we been able to postpone operation, such treatment would have proved unnecessary. Whenever it was possible the effects of routine treatment were observed for a few hours before special treatment was given.

Group A. Forty-nine Preoperative Cases of Slight Shock.

[2] Jour. Am. Med. Assn., vol. lxx, p. 1219–1220.

Entrance blood-pressure varied from 60 to 100 systolic. Routine treatment (rest, warmth, forced fluids by mouth and rectum) was instituted. Three of the cases died from infection. All of the others responded promptly to the treatment as outlined, the blood-pressure rising to normal within two hours. All stood operation well and were eventually transferred from the shock ward in good condition.

Group B. Sixteen Cases of Extreme Shock. In every instance the patient's general condition and the meager history pointed to a condition of shock for a number of hours. The extremities were cold, skin clammy, pulse rapid, thready, in several instances not palpable; pallor was extreme; restlessness more or less marked; respiration rapid and shallow; temperature subnormal. Entrance blood-pressure averaged around 60 systolic, and in five cases could not be read at all. It was evident that all the patients had lost considerable blood, but no readings were made to determine the extent of hemorrhage.

In addition to routine treatment all the various forms of special treatment were tried on this group. Seven cases were treated with gum-salt solution alone. In each case 500 c.c. of the solution was given at once, followed in one instance by 500 c.c. more at the end of an hour, and in another instance by 800 c.c. normal saline solution. Five cases were treated with both gum-salt solution and citrated blood. About 500 c.c. of the gum salt given at once followed within one hour by from 400 to 700 c.c. of blood. Finally there were four cases in which blood transfusion alone was done. From 600 to 700 c.c. citrated blood was given within half an hour after admission.

None of the patients in this group responded in any way to the treatment given, and all died within three hours following admission.

Group C. In contrast with the above group, consider a group of 36 cases of moderate shock, with a blood-pressure of 80 or below, in which the treatment consisted of nothing but rest, warmth and fluid by mouth and rectum. None of these cases had lost much blood nor was there evidence of infection. Shock was probably due in a very large measure to cold, exposure, lack of food and fluids. In this group the following 2 cases seem worthy of special mention.

Case I.—Gunshot wound of the abdomen, five days post-operative. The patient had been in the ambulance practically the entire day. Condition on entrance: cold; clammy; pulse thready; color good; systolic blood-pressure 60; diastolic not readable; temperature subnormal. Active measures were taken to warm the patient up, and within two hours after admission his blood-pressure rose to 110 and within twenty-four hours he was able to be transferred to another ward.

Case II.—Gunshot wound of left arm, preoperative, fourteen hours in an ambulance. Condition on entrance: patient cold;

pulse thready, barely palpable; slight pallor. Patient had been wrapped in wet blankets, and his clothing also was wet. Entrance blood-pressure 60. Treatment consisted of warmth and forced fluids by mouth. Within two hours blood-pressure rose to 85 and in four hours to 90. Patient sent to operating room; amputation of the left arm; blood-pressure immediately after operation 90; within twelve hours 110. Within twenty-four hours patient was able to be transferred to another ward.

The average entrance systolic blood-pressure in the remaining cases of this group was between 70 and 75, and all responded very favorably within four to six hours.

Group D. A group of 24 cases of moderately severe shock. In this group all the forms of special treatment were tried in addition to the regular routine measures. This was done not because we made any particular attempt to experiment on manner of treatment but because the group, as a group, presented such a variety of problems. In order to call attention to these problems the cases will be subdivided into groups according to the type of treatment.

Subgroup 1. Case I.—Gunshot wound of leg; extremities cold; pulse thready, rate 118; blood-pressure 90; 500 c.c. of gum-salt solution given, with rise in blood-pressure to 98 within one hour. Thigh amputation for beginning gas-bacillus infection. Returned to shock ward; blood-pressure 62; 500 c.c. gum salt solution given, followed by a rise in blood-pressure to 70 in four hours, 80 in seven hours, and 110 within about twenty hours. Patient receiving warm saline solution by rectum constantly. Patient transferred from shock ward in good condition.

Case II.—Gunshot wound of right arm and shoulder; extremities cold; pulse 120, poor quality; blood-pressure 60 to 70; 500 c.c. of gum-salt solution given, with rise in blood-pressure to 80 within six hours; sent to operating room; shoulder amputation; returned to shock ward; blood-pressure 70; 500 c.c. of gum-salt solution given, followed by a gradual rise in blood-pressure, reading 110 within about twenty hours. Patient transferred from shock ward in good condition.

Case III.—Gunshot wound of both legs; extremities slightly cold; pulse 90, fairly good quality; blood-pressure 88; 500 c.c. gum-salt given; rise in pressure within three hours to 98. Operation, extensive débridement of both legs; returned to shock ward with blood-pressure of 92, which gradually rose to 110 within twenty hours. Patient transferred from shock ward in good condition. Gum-salt solution apparently acted very well in tiding this patient over the operation. There was not much loss of blood, neither was there evidence of infection.

Case IV.—Gunshot wound of legs; received in shock ward in apparently good condition; extremities warm; pulse 120; blood-pressure 110; patient seen by surgical chief, who decided that the

case was not urgent and could wait for operation. Patient sent to operating room fourteen hours after admission; blood-pressure had already fallen to about 95 and gas gangrene had begun. High amputation of left leg. Patient returned to shock ward; blood-pressure 90, which fell in two hours to 50; 500 c.c. of gum-salt solution given, followed by a rise in blood-pressure to 70 in two hours, with no further rise in four hours. Gas-bacillus infection apparent in other leg. Six hours after operation patient died.

CASE V.—A case in which it was felt at the time that gum-salt solution had perhaps done harm. A postoperative case, thigh amputation for beginning gas gangrene; admitted to the shock ward in apparently good condition, except that the blood-pressure was only 60. Within two hours the pressure rose to 88, but within four hours fell to 70. At this time 500 c.c. gum-salt solution given. The administration of the gum solution was followed by a severe chill and the patient died within two hours. This was the only case in which a severe chill followed the administration of gum-salt solution. It might well be argued in this case that the fluctuating blood-pressure was an evidence of severe infection, and that therefore the case was unsuitable for intravenous medication.

It will be noted in the above group of 5 cases that there was little or no hemorrhage. In Cases I, II and III gum-salt solution served well to tide the patient over the period of operation, even though in 2 of the cases there was some evidence of infection. Case IV is a case of severe infection and intravenous gum salt had little or no effect on the course of the disease. In Case V we are left in doubt as to whether or not gum-salt solution hastened death. In the opinion of the writer it did not, because there have been many instances in which rapidly spreading gas-bacillus infection has caused sudden death.

Subgroup 2. CASE I.—Gunshot wound of the abdomen; postoperative; considerable hemorrhage; pulse 164; blood-pressure 64; 500 c.c. of gum-salt solution given; fall in blood-pressure within three hours to 60; 200 c.c. of blood given followed by a rise in blood-pressure to 68 within six hours; 450 c.c. more of blood given followed by a slow but constant rise in pressure to normal. Constant rectal saline during first twelve hours Patient was transferred from shock ward in good condition.

CASE II.—Gunshot wound of right arm. Postoperative; considerable hemorrhage on operating table. On admission to shock ward blood-pressure 50; pulse 130; skin warm; 500 c.c. gum-salt solution given within one hour of admission. Pressure down to 68 in one hour and fluctuated between 68 and 60 during the next two hours; 200 c.c. blood given, with a rise in pressure to 70 within two hours; 450 c.c. blood given, with a rise in pressure to 105 within four hours. Patient eventually transferred in good condition.

Shock in above two cases was due to hemorrhage. Gum-salt

solution apparently did little good, but, as a matter of fact, probably helped considerably to tide the patient over until a complete transfusion could be done. Case II illustrates the great value of the citrate method in war conditions; 600 c.c. of blood was drawn for this patient's first transfusion, but only 200 c.c. was given him because another admission to the ward seemed to be in greater need of the remaining 400 c.c. Later it was possible to secure another donor and complete the transfusion.

Case III.—Gunshot wound of both legs; skin cold, moist; pulse thready; patient slightly restless; admission blood-pressure 74; 500 c.c. of gum-salt solution given; no change in blood-pressure in three hours; 500 c.c. more gum-salt solution given; blood-pressure rose in two hours to 85 but fell to 70 within four hours. Patient was then transfused with 300 c.c. of blood, and within twelve hours blood-pressure had risen to 110 and remained permanent. Patient developed gas gangrene in both legs, and both were amputated. Patient stood the operation well, but subsequently died of extensive gas infection.

Case IV.—Gunshot wound of the tibia; postoperative; gas-bacillus infection; admitted in poor condition; blood-pressure 84; 500 c.c. gum-salt solution given; pressure fell in four hours to 68; 400 c.c. gum-salt solution given; pressure continued to fall to 60 in eight hours; 400 c.c. of blood given; pressure rose from 60 to 108 in eight hours. Constant rectal saline. Amputation of arm necessary for gas gangrene. Following operation blood-pressure 88; 500 c.c. of gum-salt solution given, followed by a rise in pressure to 100 in twelve hours. Patient died the next day from extensive gas infection.

Case V.—Postoperative; leg amputation for gas gangrene; admitted in poor condition; blood-pressure 70; 500 c.c. of gum-salt solution given; fall in blood-pressure to 60 within three hours; 600 c.c. of blood given and pressure rose from 60 to 98 within eight hours, and then began to fall again, due to extensive bleeding from necrotic tissue in stump. 700 c.c. more blood given, but impossible to control hemorrhage, and the patient died.

Case VI.—Gunshot wound of leg and buttock; postoperative for beginning gas-bacillus infection; blood-pressure 50; 500 c.c. of gum-salt solution given, with no response in three hours; 450 c.c. of blood given and pressure rose to 100 within twelve hours. Second operation necessary; amputation of leg and extensive débridement of buttock and other leg. Pressure fell to 84, rose in next two days to 110. Third operation necessary; further débridement of buttocks. Patient stood operation well; gas gangrene controlled; patient eventually evacuated in good condition. Patient on almost constant rectal saline during entire stay in shock ward.

Case VII.—Postoperative. Amputation of right leg for gas-bacillus infection. Admission blood-pressure 80; pulse 104; skin

warm. Two hours after admission blood-pressure 75; 500 c.c. gum-salt solution given. No change in pressure for one and a half hours, when pressure fell to 50. Within an hour 600 c.c. citrated blood given; pressure began to rise at once and within four hours was 98. Patient was able to be transferred to another ward the following day, but subsequently died of infection.

Case VIII.—Gunshot wound of right thigh, with beginning gas infection; patient cold, pulseless; blood-pressure not readable; 500 c.c. of gum-salt solution given, with no results; 700 c.c. of blood given within an hour; pressure came back to 70 within four hours. Transfused a second time, with 700 c.c. of blood; pressure rose to 80 within two hours; sent to operating room; long anesthesia; patient died on the operating table.

Note that this patient was really in "shock" when sent to the operating room. It is probable that the patient's vasomotor apparatus was just able to maintain a pressure of 80, but the long anesthesia and the operation, together with a rapidly advancing infection, were more than the unstable circulation could stand.

The above subgroup of eight cases is noteworthy, because considerable hemorrhage or gas-bacillus infection or the combination was present in each case, and because special treatment in each case consisted of both intravenous gum-salt solution and blood transfusion. Mention has already been made of Cases I and II, where shock was due to hemorrhage and where infection was absent. Gum-salt solution did little good in these two cases because blood was the fluid needed and no intravenous solution can serve as a substitute for blood. In the remaining six cases severe gas-bacillus infection was present. Practically no response resulted from the administration of gum-salt solution in these cases. The response to blood was more encouraging, but eventually all the cases with one exception succumbed to the infection. This one case (VI) was remarkable, because an extensive gas-bacillus infection was eventually controlled. Note in this subgroup how the presence of infection complicates the results regardless of the form of treatment.

Subgroup 3. Case I.—Gunshot wound of leg; beginning gas infection; pulse barely felt; extremities cold; blood-pressure 70; considerable loss of blood; 600 c.c. of blood transfused; pressure rose to 100 in four hours. Operation: amputation of left thigh; patient stood operation well; transferred in good condition, but subsequently died from gas infection.

Case II.—Multiple wounds; beginning gas infection; extreme shock; pulseless; blood-pressure 70; 650 c.c. of blood given; pressure rose to 85 within three hours, during which time patient absorbed nearly two quarts of fluid by rectum. Operation: extensive débridement; following operation pressure fell to 50; 800 c.c. of saline solution given under the skin; pressure rose slightly; patient died before another blood transfusion could be done.

CASE III.—Gunshot wound of back; severe hemorrhage; extremities cold; pulse not palpable; blood-pressure 68; 700 c.c. of blood transfused, also 800 c.c. of saline solution given under the skin; pressure rose to 100 within ten hours, during which time patient absorbed three quarts of fluid by the rectum and one quart by mouth. Operation: extensive débridement. No evidence of infection. Patient stood operation well and was transferred improved.

The remaining cases of the group, IV, V, VI, VII, VIII, IX and X are here grouped together, because they are so similar to Case III, just mentioned. In none was there evidence of infection, and all had lost considerable blood. Blood-pressure, from 60 to 70. All responded very favorably to 700 c.c. of blood and all were transferred from the shock ward in good condition.

In subgroup 3 special treatment consisted of blood transfusion alone. In those cases in which shock was due to hemorrhage and in which there was no infection the response to blood was very prompt. In cases in which gas-bacillus infection was present the results were the same as in the other subgroups.

In Group D (subgroups 1, 2 and 3) cases of shock have been presented in which special treatment consisted of (1) gum-salt solution alone; (2) gum-salt solution followed by blood transfusion, and (3) blood transfusion alone. As a result of a study of these cases the following conclusions seem justified: (1) Gum-salt solution is of greatest service in cases of moderate shock when there has been little or no hemorrhage and when there is no severe infection. In cases of hemorrhage it may tide the patient over for a period, but it is not a substitute for blood. (2) Blood transfusion alone is indicated in all cases of severe hemorrhage. (3) In the presence of gas-bacillus infection neither gum-salt solution nor blood transfusion serves to halt the infection. Only the exceptional case gets well.

DISCUSSION. The importance of such simple procedures as body warmth, rest and forced fluids in the treatment of surgical shock has long been emphasized. Probably nowhere has there been better opportunity to note the good results from such treatment than in the war zone. Especially were we impressed with the way in which shock cases absorbed fluids. It was not at all unusual for a shock case to absorb four or five pints of warm saline by rectum in about an equal number of hours. Unfortunately it was impossible to keep an exact record of the fluids taken, nor was it possible to note the effect on hemoglobin. Clinically, however, we felt very strongly that the forcing of fluids either by mouth or rectum was a very important part of the treatment.

The question as to the value of intravenous gum-salt solution in the treatment of shock has been much discussed by the various workers in the A. E. F. Apparently results in general were disappointing. At first our feeling was in agreement with this opinion,

but a careful study of the cases cited does not justify this opinion. Just as there are a great many factors to be met in the problem of "shock," so all these factors must be brought out in the criticism of any given method of treatment. For the purposes of this discussion the most important considerations are (1) duration of the condition of "shock," (2) presence of infection, and (3) amount of hemorrhage.

It has often been noted that when patients have been in a condition of shock over a period of hours the organism fails to respond to any form of treatment. It would help in the problems here presented could we state definitely just how many hours each patient had been in "shock." This has not been possible. In Group I, however, we have a series of cases in which, as far as could be determined, the condition of shock had existed for a number of hours. As has been noted all forms of treatment failed in this group. It so happened that our first experiences with gum-salt solution were with patients of this group. Consequently, first impressions were far from encouraging.

The presence of infection, especially a rapid devitalizing infection like that of the gas-bacillus, greatly complicates the problem of the treatment of "shock." It will be noted in Group D that in a number of cases in which there was little response to gum-salt solution, gas-bacillus infection was present. It is true that better results were obtained in these cases when blood was also given, but even when transfusions were done the end-result was the same apart from exceptional cases. In fact, we fell into the habit of making a diagnosis of gas-bacillus infection when, for no other evident reason, the patient failed to respond properly to treatment. Gum-salt solution, therefore, cannot be condemned as an aid to treatment from the results in cases in which "shock" was complicated by gas-bacillus infection.

The most important single factor in the problem of "shock" is the question of hemorrhage, especially how much hemorrhage. In order to treat shock cases intelligently we ought to know when intravenous solutions are needed and when blood is needed. It is quite apparent that shock teams, as a rule, had no means of actually determining this fact. No intravenous solution will serve the purpose when the demand is for oxygen-carrying corpuscles. Theoretically, gum-salt solution will sustain the circulation better than normal saline solution, but gum-salt solution cannot serve as a substitute for blood. From our own experiences, and from conversations with members of other shock teams, it seems to the writer that gum-salt solution was often called upon to do just this thing.

It will be noted that those cases in which gum-salt solution did good were cases of moderate shock, with little or no hemorrhage, without gas-bacillus infection, and when the solution was given at the time of operation to tide the patients over a critical period.

No doubt if we had confined our use of gum-salt solution to this type of case, and especially to the period when the patient was on the operating table, our results would have been different. Whether or not normal saline solution would have served the purpose as well we are unable to say, since no comparisons were made in our series between normal saline solution and gum-salt solution.

Recently, Lee,[3] Robertson and Bock[4] have thrown light on the problem of when to give fluid and when to give blood, and have suggested methods of calculating total hemoglobin and blood volume. Unfortunately, we were not in a position to make these calculations until just before the Armistice, so have no figures to offer.

CONCLUSIONS. 1. The appointment of teams specially trained and equipped to treat cases of surgical shock was justified.

2. The importance of such routine procedure of treatment as rest, warmth, forced fluids by mouth and rectum is beyond question.

3. Intravenous gum-salt solution is not a substitute for blood. It has its greatest use in cases of moderate shock, with little or no hemorrhage and without gas-bacillus infection. In such cases the solution should be given just before or during operation, to tide a patient over a critical period.

4. In cases in which both blood volume and oxygen-carrying elements are needed, blood transfusion alone serves the purpose.

5. Intelligent treatment of shock can only be carried out when methods are at hand to determine when fluids are needed and when blood is needed.

6. In any criticism of methods of treatment of shock, the duration of shock, the presence of infection and the extent of hemorrhage must be considered.

7. The citrate method of blood transfusion is simple and gave uniformly good results.

HYPERGLYCEMIA IN ITS RELATION TO IMMUNITY.

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THAT the storage and mobilization of the carbohydrate molecule within the organism is a very delicately balanced condition is fairly

[3] AM. JOUR. MED. SC., No. 4, vol. clviii, pp. 570–577. The case records mentioned by Lee as coming from our service are not included in this series.

[4] Jour. Exper. Med., No. 2, vol. xxix, pp. 139–171.

well demonstrated by the recorded results of various investigations. It is known that sugar metabolism may be upset in one of two ways: One method, which produces what is probably a metabolic disturbance, was first described by Jacobsen,[1] who found a temporary hyperglycemia after the ingestion of considerable amounts of glucose. Jacobsen's method, more or less modified, has been used by many investigators[2] in studying various diseases. The results of these investigations may be summarized in the statement that hyperglycemia occurs in a number of different pathological conditions and that the type of reaction encountered is not specific for any given pathological condition.[3]

There exists another method, first recorded by Bloom,[4] by which the carbohydrate metabolism may be upset, namely, the injection of adrenalin. Adrenalin is not the only substance which upon injection is capable of inducing hyperglycemia; thus peptone[5] and various salts,[6] as well as some of the products of protein decomposition,[7] have been shown to possess the same power. The delicacy of the hyperglycemic reaction to adrenalin has been emphasized by Underhill and his co-workers, who showed that it could be accentuated or diminished by various substances. The administration of anesthetics, the physical changes undergone by the aviator and the injection of at least one mineral acid have also been described as causing a temporary increase in the blood sugar. A reaction induced, as is hyperglycemia, by so many different agents must of necessity play a most important part in the physiological and pathological processes of the organism.

One of the commonly offered explanations of the hyperglycemic reaction is that the sugar metabolism is controlled by the glands of internal secretion, and that as these are stimulated or depressed, increases or decreases in blood sugar occur. A further investigation of this explanation forms the subject of our first experiment, in which the attempt was made to simulate the condition of temporary overactivity of one or another of the endocrine glands by the subcutaneous injection of gland extracts.

Rats were used for the experiment. They were fasted for 12 hours; a blood-sugar determination was then made and followed directly by subcutaneous injection of one of the various gland extracts. Exactly 45 minutes after the injection and again 120 minutes after the injection blood-sugar estimations were repeated.

[1] Biochem. Ztschr., 1913, lvi, 471.

[2] Williams and Humphreys: Arch. Int. Med., 1919, xxiii, 537. Hamman and Hirschman: Ibid., 1917, xx, 761. Hopkins: Am. Jour. Med. Sc., 1915, cxlix, 254. Taylor and Hutton: Jour. Biol. Chem., 1916, xxv, 173. Janney and Isaacson: Arch. Int. Med., 1918, xxii, 160.

[3] Rohdenburg, Bernard and Krehbiel: Am. Jour. Med. Sc., April, 1920.

[4] Deutsch. Arch. f. klin. Med., 1901, lxxi, 146.

[5] Kuriyama: Jour. Biol. Chem., 1917, xxix, 127, 139.

[6] Underhill et al.: Jour. Biol. Chem., 1908, iv, 395; 1916, xxv, 461, 467; 1905–06, i, 113; 1911, ix, 13; 1911–12, x, 159; 1914, xix, 119; 1917, xxix, 127.

[7] Watanabe: Jour. Biol. Chem., 1918, xxxiv, 73.

The blood was obtained from the tail vein and the sugar content estimated according to the Epstein[8] method.

While the Epstein method may be objected to on the ground that it is not very accurate, it can also be maintained that, whatever the error may be, it is the same in each test, and since our results are not based upon the accuracy of determinations of small fluctuations, but are wholly relative, the error can be disregarded when repeated estimations seem well correlated. However, care must be taken that the same pipette and graduated tube are used at all three estimations with any given animal, for it has been our experience that variations of from 25 to 30 per cent. are not infrequent as between two different pipettes or graduated tubes. Neglect of this factor would, of course, introduce a grave error in the results.

The substances chosen for subcutaneous injection were commercial adrenalin hydrochloride, commercial pituitary extract (obstetrical), and saline extracts of desiccated and powdered thyroid gland, pancreas and liver. The saline extracts were made by allowing 1 gm. of the desiccated powder to macerate in 100 c.c. of physiological saline solution for 24 hours at a temperature of 10° C. The mixture was centrifuged and the clear supernatant fluid was used within 24 hours. The dosage of the saline extracts was 0.5 c.c. while that of the commercial preparations was approximately 0.25 c.c.

In another paper,[9] in which metabolic hyperglycemia was considered, it was pointed out that one of three types of reaction might follow the ingestion of considerable amounts of glucose. Since these types of reaction occur also in the hyperglycemia discussed in the present paper we shall again describe them here. In type 1 the blood-sugar values are higher at the 45-minute interval than at the zero hour, and the values at 120 minutes are as high as or higher than those at 45 minutes. With the reaction classed as type 2 the sugar concentrations are higher at 45 minutes than at the zero hour, but the values at the 120-minute interval are lower than those at the 45-minute interval. With the type 3 reaction the blood-sugar figures are lower at 45 minutes than at the zero hour and the values at 120 minutes may be lower than those at the 45-minute interval or much higher than those at the zero hour. Strictly speaking, cases occur in the type 3 group which are not hyperglycemias but hypoglycemias, the blood-sugar values never rising above the normal during the entire experiment.

In order to determine the influence of sex and age upon the various types of reaction a series of 96 rats, in which these factors were carefully recorded, was injected with adrenalin. These animals represent the adrenalin group shown in Table I. No influence attributable to these factors was demonstrable, the percentages of the various types of reaction being equally distributed irrespective as to age or sex.

[8] Jour. Am. Med. Assn., 1914, lxiii, 1667.

[9] Rohdenburg, Bernard and Krehbiel: Am. Jour. Med. Sc., February, 1920.

The numerical data of the experiment in which gland extracts were injected are given in Table I. This table records the actual number of animals in each group, the percentage of the various types of reaction found with each glandular extract and the average as well as the maximum and minimum amounts of blood sugar found at the different time intervals. The points of interest are (*a*) the wide variations between maximum and minimum in any group at any time interval, and (*b*) the relative constancy with which the various reaction types occur, there being practically no difference if the small number of animals used be considered.

TABLE I.

Gland extract.	No. of animals.	Percentage of total group.	Zero hour, mg. per 100 c.c.			45 minutes mg. per 100 c.c.			120 minutes mg. per 100 c.c.		
			Av.	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.
					Type 1						
Adrenal	32	33	135	192	90	160	206	106	190	280	108
Thyroid	4	33	141	146	122	159	180	150	194	194	154
Pituitary	3	25	132	150	100	146	156	132	153	166	134
Liver	3	25	169	186	160	180	180	172	188	190	186
Pancreas	2	17	159	160	158	178	180	176	193	202	184
					Type 2						
Adrenal	31	32	136	200	84	176	262	70	116	220	100
Thyroid	4	33	144	194	104	173	202	136	130	156	80
Pituitary	3	25	119	130	98	144	160	136	123	130	116
Liver	4	33	166	180	148	212	214	210	181	200	175
Pancreas	2	17	156	160	152	193	208	178	157	160	154
					Type 3						
Adrenal	33	34	155	240	102	129	194	80	141	240	86
Thyroid	4	33	170	210	140	130	154	104	166	224	112
Pituitary	6	50	138	160	120	116	150	90	151	196	104
Liver	5	42	180	196	166	147	178	90	187	200	160
Pancreas	8	66	188	236	158	162	204	110	144	158	122

Hyperglycemia after adrenalin injection is not new and hyperglycemia after the injection of other gland extracts has also been described recently by French investigators.[10] It is probable that the hyperglycemia after gland-extract injection is not specific but is due to the protein content of the extract, and, as we have stated before, peptone and various proteins are known to give rise to hyperglycemia. The influence of the saline used to extract the powdered gland must also be considered, and while the protocols will not be given it may be stated that in rats the injection of 0.5 c.c. of physiological saline solution does not induce a hyperglycemia. The supposed excitability of the rat, as well as the influence of from 30 to 120 seconds of ether anesthesia, which was at times used in order to enable us to hold the animals quiet, was also controlled without demonstrating a hyperglycemia caused by either condition. The experiments subsequently to be described also demonstrate that if these factors (saline injection, excitement, anesthesia) be

[10] Achard, Ribot and Binet: Compt. rend. Soc. de biol., 1919, lxxxii, 788.

the ones which control or induce the hyperglycemia, then we are confronted with the peculiar condition that these factors run parallel with the production of antibodies.

All that can be said of the experiments recorded in Table I is that they show that all of the substances used give rise to a hyperglycemia and that the type of reaction is not specific for any one substance.

TABLE II.

Gland removed.	Time after removal when tested.	Zero hour.	45 min.	120 min.	No. of animals.	Per cent. of type.
	TYPE 1					
Adrenals complete	48 hours	126	206	212	3	43
Thyroid and part of parathyroid	34 days	139	143	151	2	33
Spleen complete	24 "	0	0	0	0	
Pancreas about three quarters	33 "	130	140	140	1	17
Thymus complete	34 "	0	0	0	0	
One kidney	34 "	150	160	160	1	9
Both testes	28 "	0	0	0	0	
Both ovaries	32 "	100	120	130	1	12
	TYPE 2					
Adrenals complete	48 hours	128	223	184	4	57
Thyroid and part of parathyroid	34 days	140	164	140	4	66
Spleen complete	24 "	0	0	0	0	
Pancreas about three quarters	33 "	124	153	134	3	50
Thymus complete	34 "	140	160	130	1	20
One kidney	34 "	133	176	142	5	45
Both testes	28 "	0	0	0	0	
Both ovaries	32 "	167	171	109	5	62
	TYPE 3					
Adrenals complete	48 hours	0	0	0	0	
Thyroid and part of parathyroid	34 days	0	0	0	0	
Spleen complete	24 "	172	166	152	6	100
Pancreas about three quarters	33 "	158	130	134	2	33
Thymus complete	34 "	155	139	162	4	80
One kidney	34 "	167	138	132	5	45
Both testes	28 "	158	131	156	9	100
Both ovaries	32 "	165	158	145	2	25

The second experiment consisted of repeating in part the previous determinations, this time on animals from which one or another internal secretory gland had been removed, either partially or completely. For the purpose of releasing glycogen, 0.5 c.c. of a 1 per cent. solution of peptone in distilled water was used, all other details being identical with those previously described. Table II gives the data of this group, the number of animals, the percentage of the various reaction types, the gland ablated and the average blood-sugar figures for each time period in any given group being presented.

As in the first experiment, three types of reaction were encountered, though some of the animals apparently showed some fixation of type. All of the animals in which either spleen or testes had been removed showed type 3 reaction, and 80 per cent. of the thymus-free group also came in this class. Singularly enough removal of the gonads of the female resulted in only 25 per cent. of type 3 reaction. The most violent reaction, the degree of hyperglycemia being the criterion, occurred in the adrenal-free group, the remaining animals showing less violent reactions, with the reaction in the thyroid-free group the least marked of all. In this connection it may be recalled that Janney and Isaacson have shown that removal of the thyroid inhibits hyperglycemia.

The results of the second experiment indicate that what we have chosen to call the non-metabolic hyperglycemia is not markedly influenced by removal of any of the internal secretory glands given in Table II.

In a third series of experiments, substances of widely different characteristics were injected subcutaneously into rats, in order to determine whether the list of substances causing a hyperglycemia might not be further extended. The substances used were 1 per cent. solutions in distilled water of peptone, amino-acetic acid and urea; pure olive oil, oleic acid and glycerin. The dosage was 0.5 c.c.; the last three substances, however, were used in full strength. All other details were the same as those previously described. It will be noted that all these substances, with the exception of glycerin gave rise to a hyperglycemia. (Table III.)

TABLE III.

Substance used.	No. of animals.	Percentage of type.	Mgm. sugar per 100 c.c. blood. Zero hour.	45 minutes.	120 minutes.
Type 1					
Peptone	0	..	0	0	0
Amino-acetic acid	1	16	106	126	162
Urea	1	16	114	140	140
Olive oil	0	..	0	0	0
Oleic acid	1	16	84	130	150
Glycerin	0	..	0	0	0
Type 2					
Peptone	4	40	155	203	155
Amino-acetic acid	3	50	115	151	144
Urea	0	..	0	0	0
Olive oil	2	33	152	161	135
Oleic acid	2	33	143	178	152
Glycerin	0	..	0	0	0
Type 3					
Peptone	6	60	194	155	180
Amino-acetic acid	2	33	143	107	150
Urea	5	84	154	125	167
Olive oil	4	66	163	141	170
Oleic acid	3	50	159	124	142
Glycerin	6	100	133	132	139

A brief study was made also of the reaction following the injection of a 1 per cent. solution of urea in distilled water in man, the Lewis-Benedict method as modified by Meyers and Bailey being used to estimate the blood sugar and the time intervals remaining as for the rats. As is shown in Table IV, variations in blood sugar followed these injections, and in one instance a variation of 33 mgm. was observed.

TABLE IV.—GLYCEMIC REACTION IN MAN AFTER INJECTION OF UREA.

Substance.	Zero hour.	45 minutes.	120 minutes.
Urea: Dose: 2 c.c. 1 per cent. solution . .	129	112	96
	80	110	84
	92	120	102
	106	86	74
	136	129	126

Constancy of reaction type not being demonstrable with any of the substances used, our next experiment consisted of repeated injections into the same animal of different gland extracts. As is shown in Table V, even in the same individual the type of reaction is not constant when the substances injected are varied.

This last experiment was repeated on rabbits, the substance injected being a saline extract of desiccated fresh normal human liver obtained from a healthy man who had committed suicide. Blood-sugar estimations were made as before, at the same time intervals and by the same method as with the rats. The injection were given daily and in doses increasing by 0.25 c.c., the initial dose being 0.25 c.c. Three rabbits were used in the experiment; the data are given in Table VI.

Inasmuch as the matter can be much better shown by graphs, we have plotted in Chart 1 the varying reactions observed in rabbit 1 following the first five injections. It is evident that when the same substance is used for repeated injections the types of reaction encountered vary without rule. If, however, the figures for each zero hour on successive days be plotted as in Chart 2, which presents the averaged figures for the three animals, it becomes evident that with each repeated injection there is a gradually increasing hyperglycemia in which each succeeding low point is higher than the low point preceding. The 45-minute and 120-minute figures when plotted in the same manner also show this gradual increase in hyperglycemia.

Another series of three rabbits was injected with typhoid bacilli standardized at two billions per cubic centimeter. The injections were given subcutaneously every third or fourth day in increasing doses, commencing with 0.25 c.c., and increasing 0.25 c.c. every injection. Blood-sugar estimations were made as before, but at the zero hour and 60-minute interval only, and at the same time the agglutinin titer of the serum was tested. The data of the experiment

TABLE V.

Date, August.	Rat No.	Zero hour.	45 minutes.	120 minutes.	Type.
12	1	160	172	186	I
13		158	182	192	I
20		138	158	164	I
25		160	142	194	III
12	2	196	176	200	III
13		164	188	170	II
20		220	240	220	II
25		122	140	130	II
12	3	158	212	190	II
13		196	190	176	III
20		180	186	190	I
25		172	130	140	III
12	4	180	214	175	II
13		154	124	170	III
20		160	166	132	II
25		180	214	190	I
12	5	180	214	180	II
13		200	150	192	III
20		136	160	172	I
25		154	200	200	I
12	6	166	138	190	III
13		176	180	192	I
20		150	150	148	III
25		128	116	150	III
12	7	180	156	194	III
13		180	200	170	II
20		130	176	210	I
25		180	200	180	II
12	8	190	178	160	III
13		176	140	116	III
20		180	180	140	III
25		130	180	120	II
12	9	170	90	192	III
13		170	180	162	II
20		164	172	144	II
25		120	100	80	III
12	10	186	188	190	I
13		152	160	230	I
20		170	178	180	I
25		182	180	200	III
12	11	160	180	188	I
13		142	192	164	II
20		174	172	142	III
25		178	160	164	III
12	12	184	210	200	II
13		122	178	194	I
20		154	160	144	II
25		110	134	180	I

August 12, liver; August 13, pancreas; August 20, thyroid; August 25, Adrenals.

are given in Table VII and the average curves for the blood-sugar values and serum titer are shown in Chart 3. It is apparent that the progressive hyperglycemia and development of agglutinins run parallel, and that when the titer no longer increases in strength then the temporary hyperglycemia following each injection subsides, though the zero hour values may for a period remain high.

TABLE VI.—MGM. OF SUGAR PER 100 C.C. BLOOD.

Date.	Rabbit.	Zero hour.	45 minutes.	120 minutes.	Type of reaction.
2	1	112	212	230	I
4	1	124	40	136	III
6	1	210	204	190	III
8	1	136	65	230	III
10	1	194	196	280	I
12	1	236	250	220	II
15	1	150	150	152	III
17	1				
18	1				
19	1	210	...	190	
25	1	220	...	190	
2	2	116	340	194	II
4	2	116	48	124	III
6	2	...	220	216	
8	2	186	242	104	II
10	2	140	158	208	I
12	2	...	...	264	
15	2	220	226	240	I
17	2	240	...	260	
18	2				
19	2				
25	2	110			
2	3	65	230	234	I
4	3	156	48	112	III
6	3	220	200	200	III
8	3	170	136	156	III
10	3	170	198	214	I
12	3	152	...	136	
15	3	238	280	240	II
17	3				
18	3				
19	3	210	...	188	
25	3	115			

Another series of three rabbits was injected with 2 c.c. of a 5 per cent. suspension of sheep red blood cells, injections being made subcutaneously in uniform dosage. At stated intervals blood-sugar determinations and lytic titers were done, the time periods being the same as with the rabbits injected with typhoid vaccine. The data of the experiment are given in Table VIII and graphically shown in Chart 4. Again, it is evident that the increasing hyperglycemia follows the development of lytic substances.

Conclusions. From the experiments recorded it may be concluded that a temporary hyperglycemia accompanies the injection

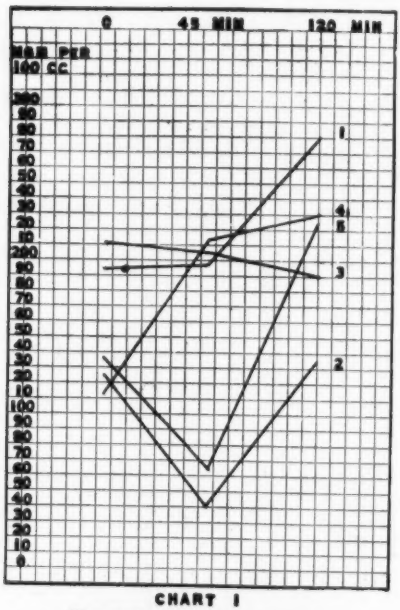

CHART 1

SHOWING DIFFERENT TYPES OF REACTION FOLLOWING SUCCESSIVE INJECTIONS OF THE SAME SUBSTANCE

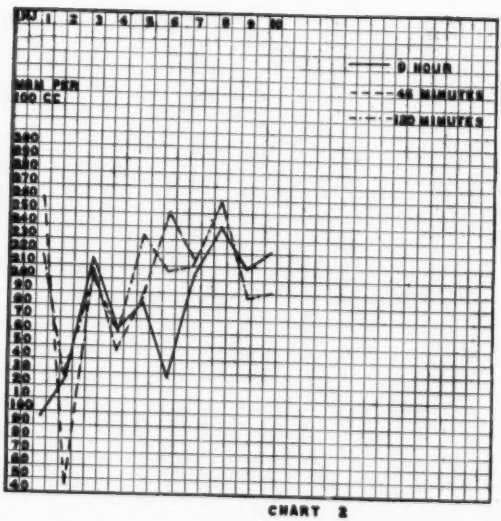

CHART 2

of a variety of organic and inorganic substances. The reaction type encountered is not specific for any given substance injected,

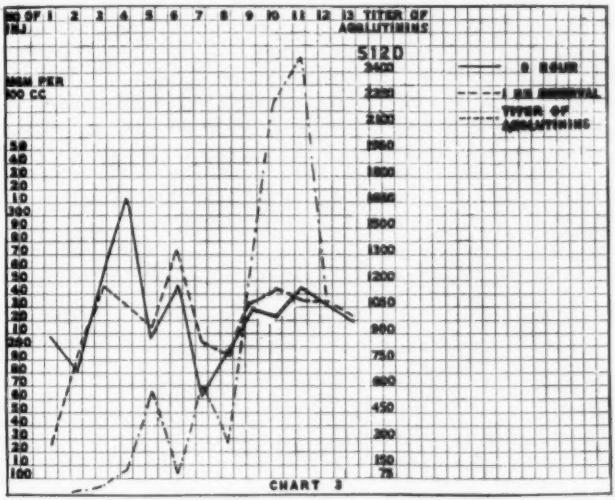

CHART 3

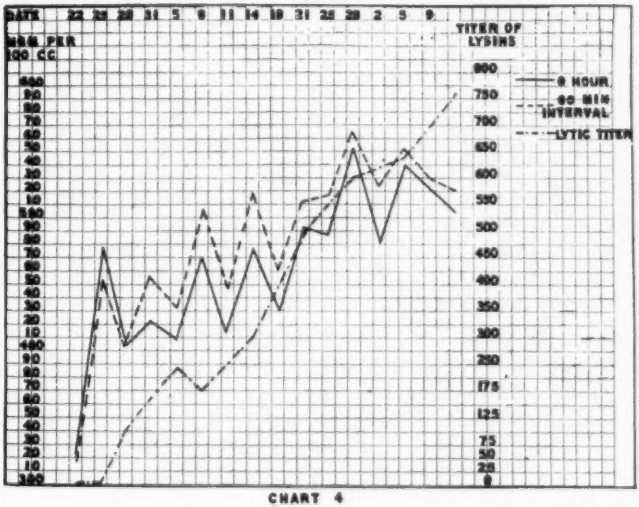

CHART 4

nor can a reaction type be said to be distinctive of lack of function of any one of the endocrine glands tested. Repeated injections of

the same substance cause a gradual rise in the blood sugar parallel to the formation of agglutinins or lysins. Irregular fluctuations occur in the sugar content of the blood from day to day, but, as shown in Chart 4, the trend is upward until the maximum titer of antibody is reached, no glycemic reaction following the further injection of the substance used. Whether this hyperglycemia is due to temperature variations which are known to follow the ingestion[11] or the injection of foreign protein,[12] or whether it is due to the breaking up of protein which occurs in the process of antibody formation, cannot at present be definitely stated.

TABLE VII.—MGM. OF SUGAR PER 100 C.C. OF BLOOD.

Date.	Rabbit.	Zero hour.	60 minutes.	Agglutinin titer.
22	1	210	130	
24	1	196	170	
27	1	188	202	80
1	1	266	260	160
5	1	210	230	320
8	1	240	280	80
11	1	120	160	1280
15	1	238	224	640
18	1	210	230	1280
23	1	220	230	5120
28	1	234	234	5120
1	1	220	230	1280
4	1	228	230	
22	2	248	144	
24	2	202	194	
27	2	226	222	20
1	2	224	236	40
5	2	200	180	1280
8	2	280	300	80
11	2	160	250	320
15	2	210	216	60
18	2	236	240	320
23	2	200	230	280
28	2	256	248	5120
1	2	244	250	640
4	2	240	244	
22	3	166	108	
24	3	146	200	
27	3	216	250	80
1	3	228	200	160
5	3	213	230	80
8	3	220	240	160
11	3	200	210	
15	3	140	144	160
18	3	240	226	80
23	3	250	270	1280
28	3	246	250	1280
1	3	228	224	5120
4	3	204	200	1280

[11] Atkinson and Lusk: Jour. Biol. Chem., 1918, xxxvi, 415.
[12] Zinsser: Infection and Resistance, New York, 1918.

The experiments here recorded show a phenomenon associated with the process of immunity which has hitherto escaped observation. An analysis of the hyperglycemia following repeated injections of the same substance indicates that the hyperglycemia is one which gradually increases in intensity up to a certain level of sugar concentration in the blood, that it keeps this level of intensity

TABLE VIII.—MGM. OF SUGAR PER 100 C.C. OF BLOOD.

Date.	Rabbit.	Zero hour.	60 minutes.	Lytic titer.
22	1	380	316	
25	1	480	480	
28	1	428	440	100
31	1	436	456	200
5	1	408	460	200
8	1	496	520	200
11	1	460	476	
14	1	480	520	400
18	1	456	468	
21	1	480	496	600
25	1	480	500	
28	1	560	588	900
2	1	520	540	
5	1	544	560	1200
9	1	536	556	
12	1	528	528	1400
22	2	336	300	
25	2	516	460	
28	2	388	376	100
31	2	420	440	100
5	2	396	400	200
8	2	480	520	200
11	2	366	420	
14	2	472	520	200
18	2	396	416	
21	2	520	540	300
25	2	508	540	
28	2	544	552	400
2	2	480	596	
5	2	516	536	300
9	2	500	500	
12	2	500	508	400
22	3	248	340	
25	3	456	420	
28	3	396	396	100
31	3	412	472	200
5	3	420	440	300
8	3	464	484	200
18	3	440	500	
21	3	480	500	600
25	3	476	516	
28	3	552	560	500
2	3	440	440	
5	3	560	560	400
9	3	536	536	
12	3	496	496	500

The blood-sugar values are considerably higher in this group because 0.05 c.c. of blood were used instead of 0.2 c.c. as with the others. The smaller the amount of blood used the higher the normal values, has been our experience.

for a short period and then returns to a normal figure even though the immune bodies are still present in the blood. The experiments further suggest that the hyperglycemia which follows the injection of substances generally supposed not to be capable of inducing antibody formation (*i. e.*, fats, polypeptids) may serve as a method for testing the reactions of the body when neither precipitins, agglutinins nor lysins are demonstrable. From a practical standpoint the absence of a hyperglycemia after the injection of a given substance known to induce hyperglycemia might be taken to indicate the point of maximum antibody production in the individual or animal in question.

OBSERVATIONS ON SOME TESTS OF PHYSICAL FITNESS.

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Certain facts of considerable interest were obtained from tests carried out in France at U. S. Base Hospital No 6 during the summer of 1918.[1] At first plans for careful work were hopefully made, but the routine became soon so overwhelming that only the initial tests could be completed satisfactorily. Because of two or three important conclusions to be drawn from these tests and from the observations that followed I am making this report.

In June and July, 1918, I took over the care of the gassed cases, chiefly those convalescent, and continued this work until after the Armistice. The first task was to organize the wards, which shortly developed into a camp of several hundred patients. By October I was swamped by 500 cases in the clinic at one time, but the routine was developed satisfactorily.

The second task and the more important was to decide at what time the soldiers were fit to return to combat duty; or when they should be reviewed by the Disability Board for assignment to special duty under the classification B-1, B-2; C-1, C-2; or for return to the U. S. A. as of Class D.

A signified fitness for combat or active normal duty.
B-1 signified temporary non-combat normal duty.
B-2 signified temporary non-combat light duty.
C-1 signified permanent non-combat normal duty.
C-2 signified permanent non-combat light duty.

As time went on during the summer, work on the "gassed" cases became organized and convalescent patients from the other hospital wards were then sent to me to benefit by the exercises, games and

[1] I wish to express my appreciation for the great assistance rendered to me by Sergeant John O. Moose.

semi-military life. Eventually, my patients included "gassed" cases, convalescents from infectious diseases, patients with healing chest wounds, effort syndrome cases and a few other neurotics. About three-quarters of the cases were discharged to Class A duty and the rest were about evenly distributed, as Class B-2, Class C-2, and Class D by the Disability Board. The work proved to be successful. Some following up of the cases was begun, but was interrupted by the Armistice. Cards were printed and given to the soldiers discharged from these convalescent and "gassed" wards to be sent back after two weeks of duty. The replies indicated generally that the method of classification was satisfactory.

Tests. I shall now describe in detail the tests which we tried out before we decided finally on the ones that were the most practical. First we made a number of tests on several groups of young soldiers of average age, height and weight. One group consisted of five normal men; one of five convalescent "gassed" soldiers; one of five effort syndrome cases; and one of five psychoneurotic "shell-shock" soldiers. The tests were those of exercise and respiration, the latter following tests the British Aviation Service was using.

The respiratory tests were:

1. Breath-holding: length of time in seconds that the breath could be held.

2. Vital capacity: the amount in cubic centimeters of air that could be expelled from the chest after a maximum inspiration.

3. Expiratory force: as determined by the height in milligrams to which a mercury column, 4 mm. in diameter, could be blown.

4. Fatigue test: the length of time in seconds that the mercury column could be held by the respiration at 20 mm. height.

5. The amount of fluid (liquid paraffin) in cubic centimeters that could be blown over from one bottle into another. This combined the fatigue test factor and the vital capacity factor. This test was not one of the British Aviation Service.

The exercise tests as planned included:

1. Climbing two flights of steps in one minute of time, fifty steps in all, each one 16 cm. high.

The pulse-rate, respiratory-rate, systolic and diastolic blood-pressures and subjective sensations were noted before the exercise, immediately at the end of the exercise and two minutes and five minutes after the end of the exercise.

2. 100-meter walk and 100-meter run (dog trot) with the gas mask on.

The pulse-rate and general condition were recorded.

3. 5-kilometer march.

The pulse-rate, blood-pressure and general condition noted before and after.

We had hoped to carry out the 5-kilometer march test with the pack on, but the routine of work prevented.

TABLE I.—SUMMARY OF RESPIRATORY AND EXERCISE TESTS IN FOUR GROUPS OF SOLDIERS: NORMAL; CONVALESCENT "GASSED;" "EFFORT SYNDROME," AND PSYCHONEUROSIS WITH "SHELL SHOCK." AVERAGE FIGURES.

Group.	Respiratory tests.[1]					Exercise tests.															
						Stair climbing (50 steps, each 6½ inches high) in one minute.								Gas mask on.			5-kilometer march, 1 hour.				
						Pulse-rate.		Respiratory-rate.		Blood-pressure.							Pulse-rate.		Blood-pressure in mm. Hg.		
										Systolic.		Diastolic.							Systolic.		Diastolic.	
All soldiers.	Holding breath, time in seconds.	Vital capacity in c.c.	Mercury column; expiratory force; height in mm. to which mercury column can be blown.	Mercury column; fatigue test; time in seconds, during which column kept at 20 mm.	Blow-bottle test: c.c. of paraffin oil blown from one bottle into another.	Increase (pulse-rates).	Decrease after 2 minutes' rest.	Increase (respiratory rate).	Decrease after 2 minutes' rest.	Increase in mm. Hg. (systolic pressure).	Decrease after 2 minutes' rest.	Change at once (diastolic pressure).	Change after 2 minutes' rest.	At rest.	After 100-meter walk.	After 100-meter run (dog trot).	Before.	After.	Before.	After.	Before.	After.
Normal, 5	73	4720	157	63	154	19	21	2	2	11	13	−8	+1	81	92	128	71	97	127	125	85	86
British Aviation figures (normal)	66	4000	110	52 Held at 40mm.																	
Effort syndrome, 5	41	3250	64	21	81	28	30	9	6	17	10	−5	+6	87	115	144					
Convalescents from gassing, 5	32	2840	71	14	80	17	18	5	4	13	13	+2	0	76	101	128	72	88	105	107	68	77
Neurotics ("shell shock"), 5	13	2240	23	6	31	19	17	17	5	18	17	+1	3+	Because of nervousness could not keep masks on								

[1] The figures are the averages of three trials in each respiratory test. This applies also to the four other tables.

TABLE II.—DETAILED TESTS IN FIVE NORMAL SOLDIERS.

Group.	Respiratory tests.					Exercise tests.															
						Stair climbing (50 steps, each 6½ inches high) in one minute.								Gas mask on.			5-kilometer march, 1 hour.				
						Pulse-rate.		Respiratory-rate.		Blood-pressure.							Pulse-rate.		Blood-pressure in mm. Hg.		
										Systolic.		Diastolic.							Systolic.		Diastolic.	
All soldiers.	Holding breath, time in seconds.	Vital capacity in c.c.	Mercury column; expiratory force; height in mm. to which mercury column can be blown.	Mercury column; fatigue test; time in seconds during which column kept at 20 mm.	Blow-bottle test; c.c. of paraffin oil blown from one bottle into another.	Increase (pulse-rates).	Decrease after 2 minutes' rest.	Increase (respiratory rates).	Decrease after 2 minutes' rest.	Increase in mm. Hg. (systolic pressure).	Decrease after 2 minutes' rest.	Change at once (diastolic pressure).	Change after 2 minutes' rest.	At rest.	After 100-meter walk.	After 100-meter run (dog trot).	Before.	After.	Before.	After.	Before.	After.
J. F. L. Age, 25 years; height, 5 ft. 8 in. (173 cm.); weight, 155 lbs. (70.5 kgm.)	85	5100	250	87	250	12 68–80	12 80–68	2 14–16	+2 16–18	10 120–130	12 130–118	0 90–90	−2 90–88	84	90	124	78	80	135	128	85	80
W. J. B. Age, 25 years; height, 5 ft. 10½ in. (179 cm.); weight, 199 lbs. (90.5 kgm.)	60	3800	250	36	150	26 70–96	24 96–72	8 24–32	8 32–24	7 118–125	8 125–117	−8 90–82	+3 82–85	96	104	140	72	112	130	120	90	88
P. C. Age, 27 years; height, 6 ft. (183 cm.); weight, 195 lbs. (88.6 kgm.)	57	5300	110	42	100	22 76–98	30 98–68	4 16–20	4 20–16	25 125–150	20 150–130	−10 75–65	0 65–65	76	96	140	64	105	126	125	70	75
C. S. G. Age, 29 years; height, 5 ft. 11½ in. (181 cm.); weight, 149 lbs. (67.7 kgm.)	90	5000	95	90	140	14 74–88	16 88–72	−4 24–20	+1 20–21	8 110–118	13 118–105	−12 92–80	0 80–80	74	80	114	70	84	120	118	87	90
J. O. M. Age, 30 years; height, 5 ft. 9 in. (175 + cm.); weight, 165 lbs. (75 kgm.)	76	4350	80	60	130	20 68–88	24 88–64	2 16–18	2 18–16	4 120–124	10 124–114	−10 90–80	+5 80–85	75	88	120	72	104	125	135	92	95

TABLE III.—DETAILED TESTS IN FIVE SOLDIERS WITH MILD "EFFORT SYNDROME."

Group.	Respiratory tests.					Exercise tests.													
						Stair climbing (50 steps, each 6½ inches high) in one minute.								Gas mask on.			5-kilometer march, 1 hour.		
						Pulse-rate.		Respiratory-rate.		Blood-pressure.							Pulse-rate.	Blood-pressure in mm. Hg.	
										Systolic.		Diastolic.						Systolic.	Diastolic.
All soldiers.	Holding breath, time in seconds.	Vital capacity in c.c.	Mercury column; expiratory force; height in mm. to which mercury column can be blown.	Mercury column; fatigue test; time in seconds during which column kept at 20 mm.	Blow-bottle test: c.c. of paraffin oil blown from one bottle into another.	Increase (pulse-rates).	Decrease after 2 minutes' rest.	Increase (respiratory rates).	Decrease after 2 minutes' rest.	Increase in mm. Hg. (systolic pressure).	Decrease after 2 minutes' rest.	Change at once (diastolic pressure).	Change after 2 minutes' rest.	At rest.	After 100-meter walk.	After 100-meter run (dog trot).	Before.	After.	Before.	After.	Before.	After.
N. Heart and lungs normal	48	3400	65	17	37	14 86–100	16 100–84	18 22–40	16 40–24	20 100–120	5 120–115	−12 80–68	+4 68–72	116	122	184						
R. Heart and lungs normal	70	4700	70	43	57	20 72–92	32 92–60	4 20–24	0 24–24	16 98–114	14 114–100	−9 75–66	+12 66–78	72	100	120						
L. Heart and lungs normal	35	3450	130	10	60	44 72–116	32 116–84	8 16–24	2 24–22	34 126–160	14 160–146	0 82–82	+8 82–90	60	120	130						
McK. Heart and lungs normal	42	3350	100	35	160	24 88–112	28 112–84	10 22–32	10 2–22	14 116–130	16 0–114	−4 66–6	+6 2–68	78	112	156						
R. Heart and lungs normal; very neurotic	10	1350	40	0	8	40 80–120	40 0–80	3 15–18	2 8–16	2 136–138	0 8–138	0 72–72	0 2–72	108	120	129						

Average weight and height.

TABLE IV.—DETAILED TESTS IN FIVE SOLDIERS CONVALESCENT FROM "GASSING."

Group.	Respiratory tests.					Exercise tests.															
						Stair climbing (50 steps, each 6¼ inches high) in one minute.								Gas mask on.			5-kilometer march, 1 hour.				
						Pulse-rate.		Respiratory-rate.		Blood-pressure							Pulse-rate.		Blood-pressure in mm. Hg.			
										Systolic.		Diastolic.							Systolic.		Diastolic.	
All soldiers.	Holding breath, time in seconds.	Vital capacity in c.c.	Mercury column; expiratory force; height in mm. to which mercury column can be blown.	Mercury column; fatigue test; time in seconds during which column kept at 20 mm.	Blow-bottle test: c.c. of paraffin oil blown from one bottle into another.	Increase (pulse-rates).	Decrease after 2 minutes' rest.	Increase (respiratory rates).	Decrease after 2 minutes' rest.	Increase in mm. Hg. (systolic pressure).	Decrease after 2 minutes' rest.	Change at once (diastolic pressure).	Change after 2 minutes' rest.	At rest.	After 100-meter walk.	After 100-meter run (dog trot).	Before.	After.	Before.	After.	Before.	After.
V. Mustard gas 2 weeks ago; dyspnea, weakness and dizziness; burn of neck; no cough; lungs clear	7	2000	50	4	20	12 86–98	12 86	6 36–42	6 36	10 104–114	14 100	−6 74–68	−10 58	72	130 Faint	Not tried	76 Fell	112 out	100 for	102 rest	72	78
W. N. Mustard gas 10 days ago; dyspnea, skin burns, conjunctivitis; lungs clear	19	2500	50	18	50	14 88–102	26 76	10 22–32	6 26	10 96–106	2 104	+8 60–68	+16 84	84	112	148	66 Fell	84 out	100 for	102 rest	64	68
T. M. B. Mustard gas 2 weeks ago; cough, hoarseness, burns of scalp; heart and lungs clear	23	2600	50	10	65	30 90–120	22 98	3 21–24	5 19	18 112–130	26 104	0 80–80	0 80	84	90	130	84	90	116	125	80	98
C. C. Phosgene gas 10 days ago; dyspnea and slight cough; heart and lungs clear	83	4000	200	25	180	18 58–76	22 54	0 20–20	1 19	9 103–112	7 105	−2 60–58	+2 60	56	72	104	52 Excellent	63 t co	104 ndit	104 ion	60	70
J. E. H. Mustard and phosgene gases 2 wks. ago; cough, hoarseness, neck burns; heart and lungs clear	29	3100	50	11	40	10 84–94	14 80	5 19–24	5 19	20 90–110	16 94	+10 50–60	−8 52	82	100	130	84 Good	92 cond	107 ition	102	62	70

TABLE V.—DETAILED TESTS IN FIVE SOLDIERS WITH THE "SHELL-SHOCK" TYPE OF PSYCHONEUROSIS.

Group.	Respiratory tests.					Exercise tests.															
						Stair climbing (50 steps, each 6½ inches high) in one minute.								Gas mask on.			5-kilometer march, 1 hour.				
						Pulse-rate.		Respiratory-rate.		Blood-pressure.							Pulse-rate.		Blood-pressure in mm. Hg.			
										Systolic.		Diastolic.							Systolic.		Diastolic.	
All soldiers.	Holding breath, time in seconds.	Vital capacity in c.c.	Mercury column; expiratory force; height in mm. to which mercury column can be blown.	Mercury column; fatigue test; time in seconds during which column kept at 20 mm.	Blow-bottle test; c.c. of paraffin oil blown from one bottle into another.	Increase (pulse-rates).	Decrease after 2 minutes' rest.	Increase (respiratory rates).	Decrease after 2 minutes' rest.	Increase in mm. Hg. (systolic pressure).	Decrease after 2 minutes' rest.	Change at once (diastolic pressure).	Change after 2 minutes' rest.	At rest.	After 100-meter walk.	After 100-meter run (dog trot).	Before.	After.	Before.	After.	Before.	After.
Hu. Shell shock 1 month ago; very shaky; heart and lungs normal	7	2450	30	0	15	0 92–92	4 2–88	30 22–52	0 2–52	15 150–165	15 5–150	+25 85–110	−10 0–100	Not attempted because of condition			very nervous				
A. High explosive concussion 1 month ago; slightly tremulous; heart and lungs normal	19 By great urging	1200	18	5	35	28 76–104	16 4–88	19 21–40	12 0–28	8 110–118	8 8–110	0 75–75	0 5–75		"		"		"		
Ho. Shell shock 2 weeks ago; deaf, dumb and very tremulous; heart and lungs normal	9	1400	35	12	25	22 90–112	20 2–92	12 20–32	8 2–24	22 128–150	20 0–130	−4 78–74	+6 4–80		"		"		"		
Re. High explosive concussion 3 weeks ago; slightly tremulous; heart and lungs normal	13	4300	40	10	30	−4 116–112	16 2–96	2 22–24	2 4–22	36 120–156	32 6–124	−13 98–85	+13 5–98		"		"		"		
Co. High explosive concussion 10 weeks ago; nervous and dyspneic; heart and lungs normal	18	1850	34	5	10	50 70–120	28 0–92	20 20–40	4 0–36	10 125–135	11 5–124	−5 90–85	+9 5–94		"		"		"		

Discussion of Results. From the tables it is obvious that the cases most strikingly limited in capacity in nearly all of the tests were the "shell-shock" cases of psychoneurotics. Incidentally the convalescents from acute infectious disease, as a rule, did well in the exercises or games tried and went back to duty more quickly than any of the others, provided there was no pronounced neurotic element as an additional factor. It always proved of extreme importance to look for nervousness in all cases convalescent from any condition. Such nervous cases, although apparently recovered, generally responded poorly to the tests, and really were not fit. Such people were often bright, capable of careful mental work, but not for the strenuous physical war game. Race seemed often a factor.

All these tests appeared to be much more tests of the fitness of the nervous system than of the heart and lungs *per se*. To stimulate convalescence and to obtain an excellent test for malingering (which was usually of the unconscious type and not infrequently found), base-ball games were held about twice a week, the wards playing against each other, and as many substitutes used in the game as possible. The medical officer kept score on the side lines, thus closely following individual players. Some of the games were exceedingly close and interesting, and usually the men in the midst of the play forgot their symptoms. Some of them showed themselves easily fitted who had been complaining previously a good deal, while others were obviously exhausted by dash to the first or second base, for example. Games such as these, followed closely, prove an excellent stimulus as well as a test for physical fitness.

The test which we finally employed as the best, taking into consideration exertion, excitement and the need of economy of time and effort on the part of the medical officer, was the 100-meter run with the gas mask on. The run provided the exertion and the gas mask the mental spur. Bad general appearance, breathlessness, pain, faintness, cough, extreme tachycardia and exhaustion were the conditions looked for at the finish of the run and helped decide on the fitness of the individual. This test was used on about 2000 soldiers.

There is one further observation that I should like to make. Many of the soldiers, I should hazard probably one-third, sent down to our Base Hospital as gassed, showed only nervousness when they reached the hospital. It is quite likely that that was all that was troubling many of the A. E. F. who said that they had been "gassed."

Summary. 1. Various tests, respiratory and exercise, are described which were applied in U. S. Base Hospital No. 6, A. E. F., to small groups of normal soldiers, convalescent "gassed" soldiers and to neurotics of the "effort syndrome" and "shell-shock" types.

2. The 100-meter run with the gas mask on was the test finally chosen as the most practical for use at U. S. Base Hospital No. 6 in determining the fitness of the soldier to return to combat duty.

3. All the tests proved to be tests rather of stability of the nervous system than of cardiac and pulmonary condition *per se:* the more nervous a man the poorer his reaction.

4. One of the most important applications to civilian medicine of the lessons from these tests is with respect to the vital capacity, which proved to be rather a test, as mentioned above, of nervous stability than of the condition of the cardiovascular or respiratory systems *per se,* in the groups under discussion.

LIFE-CYCLES OF THE BACTERIA AND THEIR POSSIBLE RELATION TO PATHOLOGY.

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Very early in the history of bacteriology the belief prevailed that the various morphological units were quite interchangeable, *e. g.,* rod forms easily developed into coccus forms, and *vice versa.* As bacteriological methods were improved it became evident that in the majority of instances these changes were apparent only —that when a bacterial species or type was once isolated and subsequent contamination guarded against the induction in it of cultural and biological changes was no simple matter. In other words a pure culture, under the artificial conditions of the laboratory, would "breed true" to the characteristics that had fixed its specific ranking.

As a result the theory of fixity or immutability of bacterial types has gradually supplanted the primitive view of an unrestrained plasticity of bacterial protoplasm. For the designation of the curious but fluctuating changes in form displayed by pure cultures when subjected to variations of environment we have the term polymorphism or pleomorphism, while the term involution is applied to the bizarre forms often present in old cultures. The latter were regarded as degenerated forms, usually incapable of reproduction, and as such the counterpart of a deterioration in the nutritive qualities of the medium.

For several decades these fundamental ideas have completely dominated our conceptions of bacteria in relation to disease. The simple processes of transverse fission and spore formation have been thought to embrace practically the entire truth concerning the life-history of bacteria. Despite these facts, there has always existed a residuum of workers, who, unable to doubt experimental evidence, have not yet been entirely convinced that the story was so simple—

ho have felt that, bound up in some way with these curious morphological changes, were fundamental biological principles, which

when formulated might clarify many of the problems of infection that have been clouded so effectually by the terms pleomorphism and involution.

Scattered through the literature can be found instances, not infrequent, of observers who have found it necessary to invoke some sort of cyclic or phasic change, physiological in nature, to explain satisfactorily the conditions confronting them. But it is only within relatively recent years that any systematic efforts have been directed toward the solution of these problems, and the number of workers is but few indeed. It is not the intention of this paper to consider in any exhaustive way the literature of the subject but merely to attempt a preliminary integration of the more significant studies already made, with allusions to their possible bearing on some of the unsolved problems of present-day pathology and bacteriology.

The studies to which I wish to direct attention date back to 1914–15 or thereabouts and have been conducted chiefly by Hort, Löhnis and their co-workers and the writer. Hort's work[1] deals chiefly with the meningococci, the colon-typhoid-dysentery group and with typhus fever. He believes that the meningococcus, as we know it, is not the primary cause of epidemic cerebrospinal fever, because he is unable to produce the disease in monkeys by intraperitoneal injections of laboratory cultures of the organism, or, for that matter, in any other way. Flexner's intraspinal inoculations produced meningitis only, which is but one part of the disease. But even these results he considers at best inadequate and probably fallacious, on account of the enormous quantities of organisms used, lysis of which caused a toxic meningitis only. Flexner refers to the doses used as "colossal," also expressing himself as "disinclined to believe that in many of the experiments any multiplication whatever took place." Hort, furthermore, discounts the value of such meningeal inoculation in light of the ease with which meningitis is induced in monkeys by other organisms.[2]

On the other hand he shows that the cerebrospinal fluid of patients contains a filtrable virus which, in the fresh state, will initiate a continuous fever in monkeys when it does not actually cause death; but inoculation of this filtrate will then yield the meningococcus, in addition to other forms encountered in this disease, such as the well-known diplococcus of Jaeger. These results suggest to him that the virus and the meningococcus are phases in the life-cycle of one organism.

[1] Hort and Ingram: The Etiology of Typhus Fever, British Med. Jour., May, 1914. Hort: Typhus Fever, British Med. Jour., 1915. Hort, Lakin and Benians: Epidemic Cerebrospinal Fever: The Place of the Meningococcus in its Etiology, British Med. Jour., March 27, 1915 and April 24, 1915. Hort: The Relation of the Meningococcus of Weichselbaum to the True Infective Agent in Epidemic Cerebrospinal Fever, Jour. Roy. Med. Corps, February, 1916. Hort: The Life History of Bacteria, British Med. Jour., May 5, 1917.

[2] The citations and opinions here expressed of Flexner's works are Hort's.

He believes this organism, which he places among the ascomycetes, has a mycelial or bacillary stage; but adequate study of this phase has not yet been made. In this connection it is pertinent that the very large "coccoid" forms described in the spinal fluid have always been regarded as involutionary, but, as the result of warm stage studies on them, Hort believes that they are giant or spurious meningococci and that they give rise by endosporulation to the true meningococci, being inseparable concomitants of the latter. He also regards this giant form as the antecedent of a filtrable form. He is not certain that the latter develops directly into true meningococci, but it "appears, however, to form a connecting link between invisible filtrable virus and Weichselbaum's organism."

From my own viewpoint it would seem that, in order to demonstrate this contention with finality, it would almost be necessary to grow this ascomyces apart from the meningococci and to show that it is possible for it to pass through the evolutionary cycle which terminates in true meningococci and the virus. He has also shown that certain members of the colon-typhoid-dysentery group reproduce themselves in other ways than by simple binary fission and that the life-cycle includes in some cases an invisible phase. By employing an especially acid medium he brings about aberrant morphological types which he considers physiological variants, particularly since these types maintain their "aberrancy" for several generations when transferred to their original environment.

He has rejected in his work the employment of the Barber method for the isolation of single bacterial cells, owing to its inadequacy in the presence of invisible or very minute forms. Although this contention may be justified in cultures associated with perfectly demonstrable filtrable forms, I feel that the cultures should be started from single cells of the strain in its non-filtrable stage, if it has such a stage. At any rate, I have adopted this criterion in my own studies, if for no other reason than to forestall criticism, undoubtedly legitimate, especially in the present unsatisfactory state of knowledge of the filtrable forms and their relation to the larger forms.

Löhnis[3] in a preliminary study attacks the subject entirely from the morphological side, with the exception of some filtration experiments not yet complete. He states that all bacteria studied have been found to alternate in an organized and in an amorphous stage, from which stage in all cases "regenerative units" develop, and increasing in size turn into "regenerative bodies" which later become cells of normal shape. Direct union of two or more individual cells has also been observed. All bacteria are found to multiply, not only by fission, but also by the formation of "gonidia," which

[3] Life Cycles of the Bacteria (Preliminary Communication), Jour. Agricultural Research, July 31, 1916.

usually first become regenerative bodies, but sometimes grow directly to full-sized cells. The gonidia may be liberated either by complete or partial dissolution of the cell wall, or may develop while still united with their mother cell. A more analytical review of his work will not be entered into here, inasmuch as his study concerns itself with B. azotobacter, which, of course, is non-pathogenic. The biological principles involved, however, are the same, and for this reason his work is of suggestive import. Confirmations of a physiological nature he promises for subsequent papers.

The work of Ferran[4] and of Much[5] on the tubercle bacillus is also deserving of mention in this connection. The work of the former extends over the past two decades, and he has concluded that this organism includes in its life-history three distinct stages: First, the alpha bacillus, which is non-acid-fast and which he believes has very distinct immunizing properties in the early stages of the disease. The second stage is represented by the well-known non-acid-fast but Gram-positive granules of Much, and the third stage is the tubercle bacillus as ordinarily considered. In connection with the supervirulence attributed by Much to his granules, it is of value to recall again what has become a very common experience: that acid-fast bacilli often utterly fail of demonstration in material that on inoculation produces a virulent form of tuberculosis. Furthermore, heating the material to 80° C. renders it innocuous, proving that the result cannot be accounted for on the spore basis.

The writer's work has been an outgrowth of studies with the so-called B. hodgkini and related diphtheroid strains, although fusiform bacilli and streptothrices have also occupied my attention. I am attempting to attack the problem not only from the morphological and cultural sides, but from the immunological and pathological aspects as well.

My first study dealing with the phenomena in question appeared in 1917,[6] being a consideration of remarkable morphological and biological changes in a diphtheroid organism whereby the bacillary form was transformed into a diplococcus form, having somewhat different characteristics from the bacillus. One of the earliest changes observed in the bacillus was a gradual concentration of the chromatin granules, which in some cases went so far as to form a single large giant coccus. Long filamentous forms suggestive of the higher organisms were sometimes observed. The press of other features of this study precluded a more detailed investigation of the significance of these coccoids, which often assumed a size of

[4] Travaux sur la Nouvelle Bacteriologie de la Tuberculose, Barcelone Imp, "La Rensixensa," 1913, 13.

[5] Beit. z. Klinik d. Tuberculose, 1907, viii, 85–357, 368; 1908, xi, 67; 1913, supplement, vol. vi.

[6] A Study of the Diphtheroid Group of Organisms, etc., Jour. Bacteriol., 1917, Nos. 2, 3 and 4, vol. ii.

5 or 7 μ. The diplococcus phase of this organism reproduced itself as such and the whole phenomenon strongly suggested a mutation; but from the fact that under certain conditions the bacillary form again appeared, I did not then feel justified in regarding it as such. I should add that, when in the diplococcus form, this organism not only appeared as a streptococcus but was related pathogenically and immunologically to a certain non-hemolytic type, and I concluded that a biological linking exists between these two groups.

During the experiments I occasionally observed that the organism was filtrable. This feature of the work also had to be put aside for later study. All these rather unusual phenomena suggested to me at the time that some phasic or cyclic change might later become a necessary explanation, though I preferred to go no further in interpretation than an extreme pleomorphism. My subsequent studies with this and related organisms have convinced me that such an explanation is quite inadequate for the scope of the changes involved.

In an experimental study of a case of generalized streptothricosis[7] I have shown that a filtrable form was present in the blood, which, however, when cultivated grew as a diplococcus, the latter being experimentally changed to the filamentous or branching form. A granular or diphtheroid form was also isolated which could be changed into large coccoids, and from these the filamentous form again developed. I have regarded these separate entities with distinctive characteristics as stages in the life history of a single organism. Preliminary to these transformations the organism usually went into the giant coccus phase, which has been frequently observed among diphtheroid bacilli. I have brought forward presumptive evidence to show that these coccoids are not involution or pleomorphic, as ordinarily considered. Warm stage observations correlated with protozoal stains have developed evidence that they are capable of a very complex series of changes connected with reproduction of various stages of the organism not the least important of which being the filtrable phase found in the blood stream.

Another separate order of filtrable body or gonidium was described for the diphtheroid stage. These gonidia originated apparently between the chromatin granules. I have regarded them as comparable with Much's granules of the tubercle bacillus. Although their pathogenicity will be described in a future paper, I may anticipate to the extent of saying that they were definitely virulent under conditions that showed the bacillary phase to be quite innocuous.

The branching phase also gave rise to filtrable granules by budding, which was of special interest in that they could not be culti-

[7] Mellon, R. R.: Contribution to Bacteriology of a Fusospirillary Organism, with Special Reference to its Life History, Jour. Bacteriol., 1919, iv, 505–536.

vated beyond the first generation. This, to my knowledge, is the first evidence that trichomyces infections may have a filtrable phase; and it may explain our inability in the past to infect experimental animals with members of this group. In a paper entitled "The Prevalence of Trichomyces Infections in Western New York,"[8] several other cases were studied with this same idea in mind. Although the more detailed experimental studies on some of them will be given at a later time the evidence presented was in harmony with that given for the fusospirillary organism (streptothricosis).

Heinemann[9] working with B. diphtheria, was able to confirm my findings in part. He noticed that his culture was losing in toxicity, which seemed to be correlated in some way with the fact that it had assumed temporarily a coccus morphology. W. W. Browne[10] has recently described a chromogenic spirillum that lived and reproduced itself as a coccoid under altered conditions. It is of interest that it was no longer pigment-producing while in this stage and was physiologically different in other ways. It is but fair to state that Eberson[11] was not able to confirm my findings with the diplococcus transformations and vigorously refutes my work, chiefly on the ground that I had not used the single-celled isolation method for purifying my cultures. It is not the province of this paper to go further into his work and its relation to my own; suffice it to say that in forthcoming communications I shall show by the use of the single-celled method that the facts as I presented them were essentially correct, and will demonstrate also, more completely than has yet been shown, the mechanism of these changes with their relation to bacterial life-cycles and to mutation and variation among the bacteria.

Relation of these Studies to the Problems of Pathology. From the strictly utilitarian standpoint the origin of the various races of bacteria may be of little moment. As one man expressed it "We know that the diphtheria bacillus as such produces a toxin that can be neutralized, and whether or not it is a stage in the life-cycle of something else is of scant interest to human pathology." As those of us who are most interested in such subjects develop them further, I trust that such a viewpoint will have progressively fewer supporters than at present. This tendency of the purely medical bacteriologist to interest himself solely in pathogenic organisms has been particularly unfortunate in many ways, not the least being an indifference to some of the broader concepts of biology, little realizing that their application might bring him much

[8] Mellon, R. R.: The Prevalence of Trichomyces Infections in Western New York, Am. Jour. Med. Sc., April, 1919, No. 4, clvii, 540.

[9] Jour. Bacteriol., No. 4, ii, 361–363.

[10] Program of Annual Meeting of Society of American Bacteriologists, Boston, 1919.

[11] Jour. Infect. Dis., 1918, xxiii, 1–42.

nearer to the solution of problems in infection that have long constituted an insuperable obstacle to the advance of "practical bacteriology."

Let us consider for a moment the relatively unexplored realm of the viruses, so called, particularly with reference to certain "accompanying saprophytes" or "secondary invaders." We know that in hog cholera the B. suipestifer is constantly present in the intestines of these animals, and their blood serum shows immune reactions to these organisms. We also know that they are present in the intestines of other healthy animals at such periods of infection which might be considered as carriers. Yet it has been conclusively shown that a filtrable virus is the exciting cause of hog cholera, with the suipestifer having no relation to the disease except as a secondary invader. An epizoötic of infectious abortion in guinea-pigs with an organism resembling suipestifer constantly present was proved by Petri and O'Brien[12] to have been caused by a filtrable organism.

It is well known that a streptococcus is a constant concomitant of scarlet fever and that immune reactions can be demonstrated in the blood of many of these cases, and streptococcic vaccines have been declared by some to have prophylactic value. Yet the streptococcus is not regarded as the primary causative agent. Likewise it has been well established that a diphtheroid organism is consistently to be isolated from the glands and blood in cases of Hodgkin's disease and certain other affections of the blood organs. Yet to date, Hodgkin's disease has not been successfully reproduced. In typhus fever practically the same set of conditions exists. The fresh-blood filtrates seem to have reproduced the disease in monkeys (Hort), whereas the incubated filtrates in which B. exanthematicis appears have relatively little effect on this animal. (Hort.)

Just what is the significance of the presence of certain specific types of organisms associated with certain diseases, in most of which they are not considered as the primary causative agent? According to the present current views of "fixity of bacterial types" they have been considered, and logically so, as purely complicating factors in the diseases in which they occur. But if we take the view, evidence for which is slowly but certainly increasing, that bacteria have other means of reproduction than simple fission, we predicate at once that their life-history can be a matter of developmental phases, in which case we are free to assume, at least, that the virus, *e. g.*, of hog cholera, may be a filtrable phase in the life-history of B. suipestifer, etc.

It would modify profoundly our conception of the causation of a disease like influenza and might open the way toward establishing the actual relation of B. influenza to the disease. Indeed, a suggestion of this sort has recently appeared in the work of Wade and

[12] Jour. Hyg., 1910, vol. x.

Manalang,[13] who have shown that certain strains of this organism can by alteration of their environment be made to branch and assume other characters usually allocated to the higher bacteria.

Such a conception would be of value in the interpretation of the peculiar symptom-complexes presented by certain conditions of obscure etiology. The striking remissions of pernicious anemia, the Pel-Ebstein febrile complex in Hodgkin's disease as well as the spontaneous and clinically deceptive retrograde changes observed in this and related diseases, might well be correlated with alternate "resting stages" and stages of activity in the life-history of organisms whose adaptability was thus mirrored.

The relapsing type of fever associated with certain spirochete infections, *e. g.*, Sp. obermeiri, might thus find explanation, although this citation may be infelicitous, owing to certain taxomonical uncertainties of these forms. It may be recalled in this connection that Noguchi found "coccoid" bodies in his cultures of pallida and, that Warthin[14] has found what might be regarded as such in tissues devoid of the typical pallida but almost undoubtedly syphilitic.

The regular periodic febrile exacerbation characterizing the streptothrix infection of rat-bite fever, and the irregularly intermittent fever of other thrix infections, following deceptive clinical cures; the strong tendency to recurrence in fusiform infections may be explained on a similar basis; for these phases of activity, if such they be, must have immunological counterparts in the host.

It is not improbable that "bacterial fastness" to therapeutic agents, and to the immunological forces of the body, can perhaps be correlated with these changes in phase. It is well known, for example, that the spirochetes that survive salvarsan treatments acquire an increased resistance. The granules of Much may be a "reply" of the tubercle bacillus to the lipases of the lymphocytes. In an unpublished study I have shown that the bacillary phase of a certain diphtheroid was Gram-positive, but the diplococcus phase was Gram-negative. These cultures were started from single cells and the strains were made of twelve-hour cultures. Thus, immunologically, phases and stages of bacterial life may have a distinct bearing on the course of a disease.

The rather constant presence of a non-acid-fast diphtheroid organism in leprosy is not susceptible at present of final interpretation. Bayon (Besson)[15] and Williams (Besson)[16] regard them as a probable stage in the life-cycle of the Hansen bacillus, while Kedrowski[17] believes he has proved that they take on acid-fast characters in the

[13] Jour. Exper. Med., No. 1, xxxi, 95–103.
[14] Personal communication.
[15] Practical Bacteriology, Microbiology and Serum Therapy, Longmans, Green & Co., London, 1913.
[16] Loc. cit.
[17] Ztschr. f. Hyg. und Infectionskrank., xxxvii, 52.

body of the animal. The relation of streptococci to poliomyelitis cannot as yet be said to have received final interpretation, although the evidence for their being the primary exciting cause is but slight. Rosenow and Towne[18] claim to have demonstrated that the small forms are derived from the larger diplococci by a double fission of the latter. The Berkefeld filtrates from paralytic monkeys have also been grown to the large forms by special methods. The evidence is chiefly morphological, and as yet is too incomplete to be in any way conclusive. They speak of "cycles of division," but in too casual a manner for one to consider that they regard the various forms as phases of bacterial life-cycles, physiologically speaking. Neither is the evidence sufficient for regarding the small forms as identical with the organism of Flexner and Noguchi. The findings are sufficiently suggestive to merit more study, paralleling as they do some of the above-related ones. Rosenow has suggested a relation between them and what is evidently the causative virus, but its purely morphological basis makes it entirely a matter of conjecture.

Tunnicliffe[19] has isolated a filtrable organism quite constantly from the early stages of measles, which can later be cultivated as a diplococcus and toward which the serum later in the disease shows immune reactions, but here, again, final interpretation is not yet warrantable. It will not avail to further multiply such examples if I assume that the object of their citation has been made clear.

Conclusions. Recent studies into the etiology of disease have made necessary a reëxamination of the theories of bacterial pleomorphism and involution. An abandonment of the terms is not advocated, inasmuch as they are doubtless applicable to truly degenerative changes. If they have been misapplied to changes of a phasic nature it is obvious that the latter should receive a representative designation and for other reasons than purely academic ones.

A modified interpretation of these morphological changes may result in the reconciliation of many diverse factors associated with infectious diseases of both known and unknown etiology.

If there exist stages of bacterial life, in the sense depicted here, there necessarily must occur a revaluation of the term "secondary invader." If we eventually regard as "genuine secondary invaders," those having definite stage relationship with the primary exciting bacterial cause of the disease, the designation will be of greatest service in the investigation of diseases of unproved origin. The idea of genuine secondary invaders should also embrace the fact of the rather constant association of a certain type of organism with certain diseases.

[18] Jour. Med. Research, vol. xxxvi, pp. 175–186.
[19] Jour. Infect. Dis., 1918, xxii, 462; Jour. Am. Med. Assn., July 13, 1918, p. 104.

A NEPHRITIC DIET SHEET.

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and

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The diet sheet given below has been found useful and convenient in regulating the protein intake of nephritic patients. The physician often has a rather definite idea of how much protein it is advisable for a patient of this class to take—or rather not to exceed—without, however, any definite idea of how to tell him just what foods and what quantities he should eat. The usual way is to advise him to take so many eggs and so much milk; or we have elaborate menus, different for each day, with a varied but precise order of dishes for each meal. With this last scheme few private households are able to cope for any length of time. Moreover, it is important that restrictions shall not be excessive and that these patients receive sufficient protein in so far as their condition permits. With this sheet we believe we can make patients readily understand a method which they can easily carry out, whereby they receive, approximately speaking, the amount of protein we think they should have and no more.

In this sheet the ordinary articles of diet have been divided into three groups: The patient is instructed that whatever foods or dishes (in the current bill of fare where he happens to be) he may wish to eat he must first find on the sheet and take only in the quantities designated as full or half-portions. He is told that if the article is found in Group I a full portion counts 1 in the score for the day; if it is found in Group II it counts 2; he must keep count and "make" the total score prescribed for him. Now the quantity of each article given on the sheet as a full portion contains approximately 4 grams of protein in Group I and 8 grams in Group II. We divide the number of grams of protein we wish the patient to have in a day by 4, and the result is the figure we must write in (in the blank space left for the purpose) to represent what his daily score should be. The protein in the portions in Group II is, of course, twice as much as that contained in those of Group I; therefore a portion or helping of a food listed in Group II scores 2 while those of Group I count but 1. Group III lists foods of so low a protein content as to be negligible. It goes without saying that foods not found on our sheet may be easily added to it. The foodstuffs listed have been selected and grouped merely on the basis of the protein content. We doubt that any of these foods are

specially harmful to the kidneys. If any should be found so they may be removed.

NEPHRITIC DIET SHEET.

Any combination of the foods listed below may be selected.
Foods not listed below must not be taken.
In Groups I and II there is a restriction in the total amount.
The foods in these groups must be served in full or half portions.
A full portion in Group I counts 1.
A full portion in Group II counts 2.
In Group III the quantity of each is not restricted, although you are urged to use discretion.

Your total score for the day should be.....
Your total amount of fluid should be.....Pints.

Do not add salt or spices to the food after it has been cooked.

GROUP I—EACH FULL PORTION COUNTS 1.

	Full portion.	Vegetables, etc.	Full portion.
Bread (white	1 av. slice	Baked beans	1 tbsp.
Bread (graham)	1 av. slice	Lima beans	1½ tbsp.
Uneeda biscuit	5 crackers	Potato, creamed (P.B.B.)	1 tbsp.
Shredded wheat	1 biscuit	Potato, mashed (P.B.B.)	1½ tbsp.
		Potato, boiled	1½ med.
Cereals.		Green peas	2 tbsp.
Oatmeal	2 tbsp.	Canned corn	2½ tbsp.
Boiled rice	3 tbsp.	Onion, boiled	3 tbsp.
Cornmeal mush	4 tbsp.	Macaroni	4½ tbsp.
Cream of Wheat	6 tbsp.	Squash, boiled	5 tbsp.
Farina	6 tbsp.		

GROUP II—EACH FULL PORTION COUNTS 2.

	Full portion.	Meats.	Full portion.
Milk	1 glass	Chicken, roast	3″ x 3″ x ¼″
Egg	1 egg	Lamb chop, broiled	¾ chop
Eggs (scrambled)	1½ tbsp.	Lamb, roast	3″ x 2½″ x ¼″
Custard (P.B.B.)	3 tbsp.	Beef, roast	3″ x 2″ x ¼″
Fish.		Beef steak, broiled	2″ x 1″ x 1″
Cod, boiled	1″ x 1″ x 1¼″		
Haddock, boiled	1½″ x 1″ x 1″		
Oysters	7 oysters.		

GROUP III—NO RESTRICTION.

Vegetables.	Fruit.	Miscellaneous.
Turnips	Watermelon	Sugar
Carrots	Plums	Syrup
Cabbage	Pears	Candy
String beans	Peaches	Honey
Cucumbers	Strawberries	Maple sugar
Cauliflower	Grapes	Butter
Celery	Raspberries	Cornstarch
Tomato (fresh)	Blueberries	Arrowroot
Tomato (cooked)	Muskmelon	Tapioca
Lettuce	Apple	Post Toasties
Asparagus	Pineapple	Maple syrup
	Prunes	Olive Oil
	Apple sauce	
	Orange	
	Grape fruit	

The sheet will probably be of the greatest usefulness in the so-called out-patient "classes," at which its meaning and use can be explained to groups of patients. One change might be made in the direction of greater simplicity. It will be seen that the size of the portions of fish and meats is a little different for each kind, but all are close to two cubic inches. It would perhaps be better to have a uniform portion for all meat and fish, that is, the lean part of a lamb chop or a piece 2″ x 1″ x 1″. This is an amount easily visualized, and a block of wood could even be cut in the requisite dimensions and shown as an object lesson.

With the varied diet which the patient will naturally choose for himself under this system he will usually get sufficient calories for his needs. That this is so will be discovered if he is told at intervals to bring in a list of the foods he has eaten on two or three days previous. When, however, his protein has been cut down to the neighborhood of 30 grams a day it may well be found that he is not getting calories enough. If so a definite daily amount of butter, cream, olive oil and sugar can be prescribed, with instructions to take them on his other food. For convenience of estimation, on the physician's own sheet the calories may be written in after each portion.

Finally, this scheme, as will be readily apparent, is based essentially on the diet chart published years ago by Arnold, which in the opinion of the writers should have met with a more general use than so far as they know, has been the case.[1] It was Arnold's great merit to point out that uniform amounts of protein can be taken by common measures in quantities of food which are about what one would naturally take as a serving. Arnold's charts, however, as we think anyone who has used them will agree, are of more service to the physician than to the patient. The scheme submitted herewith makes the data available as a guide for the patient and the physician.

We gratefully acknowledge the assistance of Miss Katharine Mitchell, formerly assistant dietitian at the Peter Bent Brigham Hospital.

ANTIPNEUMOCOCCUS SERUM (KYES'S) IN THE TREATMENT OF PNEUMONIA.[1]

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In 1911, Kyes[2] announced that he had succeeded in producing an antipneumococcus serum with high antibody content by a new

[1] Arnold, H. D.: Boston Med. and Surg. Jour., 1909, clxi, 457. Medical Communication, Massachusetts Medical Society, 1909, xxi, 631. Tr. Am. Climat. Assn., Philadelphia, 1909, xxv, 128.

[1] Read at the meeting of the Tristate District Medical Society (Wisconsin, Illinois and Iowa), Rockford, Ill., September 5, 1919.

[2] Jour. Am. Med. Assn., June 24, 1911, No. 25, lvi, 1878–1881.

method. The novelty lay in using an insusceptible host, the ordinary barnyard fowl, which circumstance allowed the use of unusually large numbers of virulent living pneumococci as antigen. It was, of course, a well-known fact in immunology that pathogenic antigen was not necessary for the production of specific antibodies, but this knowledge had not been applied in the production of antibacterial sera.

The above announcement was made after laboratory experiments, both *in vitro* and *in vivo*, had demonstrated high antibody content in the serum and its protective action in laboratory animals, as detailed by the investigator in his original paper. The next step was to determine its therapeutic value in man.

Extensive therapeutic testing is the final proof of the value of any curative serum. This truism applies with equal force to antitoxin and to antibacterial sera. In the case of the former, however, there is the additional certainty that one is dealing with a definitely standardized product, checked against known lethal doses of toxin, and this certainty is felt by the investigator both during the experimental work in the laboratory and in subsequent therapeutic testing. With a standardized product it is to be expected that definite results can be repeated. In the case of antibacterial sera, on the other hand, no accurate method of biological standardization has been devised. Protection against living organisms of varying virulence, rather than against known lethal doses of toxin, carries less conviction during the laboratory stage of investigation and makes therapeutic testing of even greater relative importance. The present report is made in this spirit. It is proper to state also that Kyes has not allowed control of production of the serum to pass from his hands pending such therapeutic testing, and that he still considers the serum in the experimental stage.

In 1918 Kyes[3] published the results of the use of his serum in the treatment of 115 cases of lobar pneumonia, controlled by a series of 538 cases, in which serum was not used, but otherwise treated under the same conditions, and during the same period of time. The mortality in the serum-treated cases was 20.8 per cent.; in the control cases, 45.3 per cent.

The next therapeutic test to which the serum was put in any large number of cases was at the Base Hospital, Camp Grant, Ill. An account of its use in the treatment of 322 cases between October 1, 1917, and September 20, 1918, has been published recently.[4] The death-rate was 7.7 per cent. While there were no control cases it was evident to the clinicians administering the serum that it had marked therapeutic value. In addition the series gave valuable

[3] Jour. Med. Res., July, 1918, No. 3, xxxviii, new series; No. 3, xxxiii, 495–501.

[4] McClellan, John H.: Jour. Am. Med. Assn., June 28, 1919, No. 26, lxxii, 1884–1885.

data concerning dosage and methods of administration and other clinical phenomena, and afforded opportunity to improve the serum further on the basis of therapeutic use. With the present report the above constituted a complete record of the use of the serum in pneumococcus pneumonia at this Base Hospital. Mention may be made also, for sake of completeness, of five recoveries from pneumococcus meningitis during the epidemic following combined intraspinous and intravenous administration of the serum.[5]

The present publication carries the record on from September 20, 1918, to May 1, 1919. It is properly divided into the epidemic period, during which it was possible to compare results in cases treated with and without the serum, and the period from the close of the epidemic until May 1, 1919, during which all cases received serum treatment.

There was very little question at Camp Grant as to the character of the infection with which we were dealing during the epidemic. The preponderating organism obtained by swab culture from the nose and throat, and by culture from the sputum, during the stage of so-called influenza, was determined after a very few days to be an organism of unusual virulence, conforming in all laboratory characteristics to the pneumococcus. The Pfeiffer bacillus was found in only a negligible number of cases. Pneumococci were obtained in pure culture, or preponderatingly, from the heart blood and organs of cases dead from pneumonia and from other forms of pneumococcus disease in a large proportion of the 198 autopsies done during the epidemic period.[6] It seemed to us that no doubt could arise as to the causative organism either in the cases of so-called influenza or of pneumonia, and that in the virulence of the organism was to be found sufficient explanation of the type of pneumonia resulting. It was presumed, therefore, that treatment with serum would demonstrate therapeutic efficiency.

Since it is proposed to compare the mortality-rates in two groups of cases, those treated with and those treated without serum, the conditions under which the serum was administered should be noted. There was no preparation for control comparison. The serum had been used routinely in the hospital and the propriety of withholding an agent of presumed therapeutic value from any cases for purposes of comparison was considered doubtful under the circumstances. But when it became apparent that there would shortly be more cases of pneumonia than serum could be furnished for, it was decided to restrict its use to cases in a single ward for ease of administration

[5] Litchfield, L.: Jour. Am. Med. Assn., May 10, 1919, No. 19, lxxii, 1345–1348.

[6] Hirsch, Edwin F., and McKinney, Marion: Epidemic of Bronchopneumonia at Camp Grant, Ill., a preliminary report, Jour. Am. Med. Assn., November 21, 1918, lxxi, 1735–1736; and an Epidemic of Pneumococcus Bronchopneumonia, Jour. Infect. Dis., June, 1919, No. 6, xxiv, 494, 517.

until more serum should become available. Its use was extended later to a second ward. Cases were admitted to these wards as fast as vacancies occurred, either directly from the receiving office or by transfer from so-called influenza wards by other individuals than those interested in or responsible for the treatment. There was therefore no possible selection of favorable cases. These wards were equipped in no essential way differently from the other pneumonia wards in the hospital. The serum was withheld from no cases in these wards. Finally, all deaths in the serum-treated group, except six that were determined at autopsy to have been due to streptococcus pneumonia, were charged against the serum, in spite of complications or accompanying diseases which might have contributed to or have actually caused death, and regardless of the length of the time between serum treatment and the time of death. Four cases admitted between September 26 and 30 died in November; two admitted September 26 died in December; one admitted September 30 died the following February.

Another circumstance especially unfavorable to the serum record should be explained. On October 1 it was decided to rearrange cases in three contiguous wards, transferring all acutely sick cases in Wards 12 and 13 to Ward 11, putting cases of apparently good prognosis into Ward 12, and convalescent cases into Ward 13. Ward 11 thereafter was to be the receiving ward for the group of three, from which patients were to progress as they improved. This was to protect patients moderately sick and conscious of their surroundings from the sight and sound of the dying. The same plan was put into operation in another group of wards a few days later, where the serum, which had now become available in larger quantity, was being used. It was proposed to extend the plan to the entire hospital, but the epidemic soon became so overwhelming that it was not carried further. Carried on in these two groups of wards without any thought of its effect on the serum record, for the serum was given to all cases admitted and transferred to these receiving wards irrespective of the stage of the disease, it is fair to state that the mortality was especially high among these transferred cases. However, these statements are not made as a basis for altering the death-rate of the serum-treated cases, and no figures have been compiled to show what might have been the death-rate if the serum had been administered to all cases on diagnosis. They are made to emphasize the fact that the circumstances were in no way made favorable for the serum-treated cases.

During the epidemic period 234 cases of pneumococcus pneumonia were treated with the serum. The number of deaths in this group was 39, a death-rate of 16.7 per cent. During the same period a total of 2064 diagnoses of pneumonia were made in the hospital. There was a total of 1088 deaths. The death-rate was approximately

52.7 per cent., but the total number of diagnoses and the total number of deaths include serum-treated cases and streptococcus cases, which must be subtracted for the purpose of this comparison.

Hirsch and McKinney,[7] in a paper previously referred to, detailed the bacteriology found at 198 autopsies during the epidemic. Streptococci were found in a small percentage. It was apparent that clinical differentiation between streptococcus and pneumococcus pneumonia had been largely impossible during the epidemic, partly because of the type of the epidemic diseases and partly because the necessary laboratory investigation for such a large number of individual cases was clearly out of the question. The total number of diagnoses of pneumococcus pneumonia recorded in the hospital, therefore, included a certain number of streptococcus cases. But since six deaths are cut out of the list of serum-treated cases because it was determined at autopsy that streptococci were the primary invading organisms, it becomes necessary to estimate a fair reduction in deaths among cases not treated with serum, few of these cases having come to autopsy. Using the same proportion as obtained in the serum-treated cases it is estimated that 140 deaths due to streptococcus pneumonia occurred among the cases not treated with serum. With the figures thus obtained the mortality in these cases, as detailed in the accompanying tabulation, is figured to have been 53.6 per cent.

The comparison I wish to submit, therefore, is a mortality of 16.7 per cent. in 234 serum-treated cases of pneumococcus pneumonia, with a mortality of 53.6 per cent. in 1684 similar cases treated in other respects by the same methods except that they received no serum. In other words the death-rate in the serum-treated cases was somewhat less than one-third that in the cases compared.

The serum was administered intravenously in all cases. Shortly before the epidemic the dose was increased from 2.5 c.c. once or twice daily to 5 to 10 c.c. twice daily, and this larger dosage was maintained during the epidemic. In a few cases as much as 30 c.c. was given daily. Commonly a total of 60 to 90 c.c. was given in cases that recovered.

As to the clinical phenomena following use of the serum little more can be said than is told in the reduction of mortality. No marked changes were regularly seen after serum administration that were not seen in individual cases not treated with serum. It was the feeling of the writer, therefore, that any attempt to tabulate symptomatic changes in the serum-treated cases for comparison with control cases would bring personal impressions into the record to such an extent that any conclusions arrived at would be open to question. Reduction of mortality, however, is a definite phenomenon. Thera-

[7] An Epidemic of Pneumococcus-Broncho-Pneumonia, Jour. Infect. Dis., June 1919, No. 6, xxiv, 594-617.

peutic value of any treatment must finally be judged by this end-result.

The *modus operandi* of the serum is, of course, of great interest but except for the fact that the serum is antibacterial any statement would be purely hypothetical. As to the so-called foreign protein reaction it should be stated that in only approximately 5 per cent. of cases was there any appreciable reaction following the serum used during the epidemic. This non-specific reaction cannot, therefore, be considered a factor in the reduction of mortality.

Following the epidemic, cases of pneumonia were atypical. Streptococcus pneumonia was much more common than during the epidemic. But pneumococcus pneumonia itself was also atypical, conforming in symptomatology neither to lobar pneumonia nor to the epidemic bronchopneumonic type, though the appearance of the lungs at autopsy was more clearly that of the latter. There was evidence that the organism was dropping in virulence (unpublished observation of E. F. Hirsch). Finally, in March and April, 1919, lobar pneumonia began to reappear. During the period, therefore, from the close of the epidemic to May, 1919, when this record closes, there was a continually changing picture of disease in the pneumonia wards. It was difficult to establish a clinical standard of differentiation of streptococcus from pneumococcus cases.

But while this period was in many ways an unsatisfactory one in which to attempt to evaluate the therapeutic effect of the serum, not only because of lack of controls but also because of the facts above set forth, it is believed that the final compilation of pneumococcus cases was accurate and that the low mortality is credited properly to the serum. There were 5 deaths among 118 serum-treated pneumococcus cases, a death-rate of 4.3 per cent.

The record of the use of Kyes's antipneumococcus serum at Camp Grant can now be summed up. 322 cases of pneumonia were treated between October 1, 1917, and September 20, 1918, with a death-rate of 7.7 per cent.; these were cases of typical lobar pneumonia. 234 cases of epidemic pneumococcus-broncho-pneumonia were treated between September 21 and November 4, 1918, with a death-rate of 16.7 per cent. which is to be compared with a death-rate of 53.6 per cent. in 1684 control cases. 118 cases were treated between November 5, 1918, and May 1, 1919, with a death-rate of 4.3 per cent.; these were atypical cases of pneumococcus pneumonia, which seemed to indicate a gradual change from the epidemic type of disease back to the type of lobar pneumonia, probably due to a falling virulence in the organism. In addition 11 cases of pneumococcus meningitis were treated, with 5 recoveries, 1 fatal case having occurred since the publication by Litchfield (loc. cit.)

EPIDEMIC STATISTICS, SEPTEMBER 20 TO NOVEMBER 5, 1918.

Total number of diagnoses	2064
Total deaths	1088
Death-rate	52.7%
Serum-treated cases	240
Streptococcus deaths subtracted	6
Pneumococcus cases	234
Pneumococcus deaths	39
Death-rate	16.7%
Non-serum cases	1824
Streptococcus deaths, subtracted (estimated)	140
Pneumococcus cases	1684
Pneumococcus deaths (see below)	903
Death-rate	53.6%
Total deaths	1088
Serum deaths	45
Non-serum deaths	1043
Streptococcus non-serum deaths (estimated)	140
Pneumococcus non-serum deaths (see above)	903

INCIDENCE, ASSOCIATED PATHOLOGY AND CLINICAL DIAGNOSIS OF CHRONIC PERICARDIAL ADHESIONS.

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The report of this investigation deals with a condition which, during the years recent and long passed, has received deliberate study from some of the most noted clinicians and pathologists, while apparently being seriously neglected by others equally noted. I refer to that pathological state characterized by an obliteration of the pericardial cavity, completely or in part, by adhesions. Associated with this there may or may not be extrapericardial adhesions. Because the adhesions associated with a pleural tuberculosis have a distinct clinical picture peculiar to this type of adhesions, we have sought, in so far as we were able, to exclude all cases possibly tuberculous from the series.

Since the study of this subject has been pursued only along lines of my own personal choice, no reference will be made to the not voluminous but rich and select literature. To the writer the two most perplexing features of this pathological state are its etiology and diagnosis. Many other intricate and interesting features surely do exist and will receive in their turn some discussion in which we may suggest that these associated features either explain the etiology or assist in rendering a diagnosis.

In the analysis here presented no definite theory as to the etiology will be advanced, as, even after a rather critical survey of the past histories of the cases representing this series, no specific etiology

could be exposed. A study of the etiology is so clearly interwoven with the associated pathology that it must be considered with the greatest advantage in association with the pathology found not only within the heart wall but within other organs as well. This clinical and pathological report is the result of the study of 30 cases of pericardial adhesions of various grades occurring in 514 consecutive autopsies at the St. Louis City Hospital. When all grades of adhesions are included there is an incidence of 5.8 per cent. represented in this series. For convenience of comparative study these cases were grouped arbitrarily into three classes: mild, moderate and extensive. From both a pathological and clinical point this arbitrary grouping is deceptive, in that it neglects the position of the adhesions which at least almost certainly determines the presence or absence of clinical signs as well as their severity when present. When classified in this manner, however, the 30 cases were grouped as: mild adhesions, 4 cases; moderate adhesions, 18 cases; extensive adhesions, 8 cases. Extensive was reserved for those cases in which the pericardial cavity was completely obliterated. In some of these cases there were also extrapericardial adhesions fixing the pericardium to the diaphragm, costal cartilages, pleura and lung or to the structures in the posterior mediastinum.

Adopting this classification reveals that of the 514 patients coming to autopsy 1.5 per cent. had extensive adhesions, 3.5 per cent. moderate adhesions and 0.8 per cent. mild adhesions. Unless the adhesions in the mild and moderate cases are almost selectively located, and especially if there are no extrapericardial adhesions, there is much doubt to be entertained as to the possibility of clinical recognition. The clinical diagnosis of the extensive adhesions seems to be assured, more especially, if there are extrapericardial adhesions of moment present.

The apparent causes of death in the 8 cases of extensive adhesions were:

Typhoid fever	3 cases
Acute endocarditis	1 "
Operation for the relief of adhesions	1 "
Carcinoma of stomach	1 "
Chronic nephritis	2 "

The apparent causes of death in the 18 cases of moderate adhesions were:

Cerebral apoplexy	2 cases
Carcinoma of liver	1 "
Carcinoma of stomach	1 "
Acute nephritis	11 "
Pulmonary tuberculosis	1 "

In the mild cases 2 died of cirrhosis of the liver and 2 from chronic nephritis.

A feature relative to the apparent cause of death is the fact that 50 per cent. of the series died from chronic nephritis, presenting apparently a possible relationship between the etiology of chronic nephritis and pericardial adhesions. In fact this is true not only of chronic nephritis but of associated pathological changes in numerous other organs. In this light a careful study of the pathology present in other organs besides the pericardium would establish somewhat the nature of the etiology at least in some general way. In the 30 cases of this series the associated changes found in the lungs and pleura were as follows:

Pleural effusion	3 cases
Chronic pulmonary tuberculosis	6 "
Chronic pleural adhesions	15 "
Chronic passive congestion	18 "

The associated changes within the heart and large vessels were:

Chronic myocardial fibrosis	15 cases
Acute endocarditis	1 "
Chronic arteriosclerosis	14 "
Chronic endocarditis	6 "

Within the entire series only one heart presented no marked changes. In this case the adhesions were termed moderate. In the liver were the following associated changes:

Chronic passive congestion	14 cases
Chronic cirrhosis	10 "
Chronic degeneration	8 "
Chronic perihepatitis	3 "
Hepatic syphilis	2 "
Livers presenting no marked changes	1 "

The spleens presented the following changes:

Chronic passive congestion	20 cases
Chronic perisplenitis	2 "
Chronic hyperplasia	2 "
Chronic atrophy	1 "
Spleens presenting no changes	5 "

The associated findings in the kidneys were in the majority of cases very extensive. The following changes were found:

Chronic nephritis	24 cases
Chronic congestion	3 "
Acute cloudy swelling	3 "
Amyloid degeneration	2 "

There were no kidneys free from pathological changes.

At once in this study one is impressed with the frequency of pericardial adhesions associated with myocardial, vascular, hepatic and renal changes, for the most part fibrotic in type. The most natural supposition is that a common etiology exists in the form of a chronic infection or intoxication. This conclusion is contrary

to those placing the pulmonary, hepatic and renal changes secondary to the pericardial state because of the accompanying cardiac insufficiency. This is also supported by the results of some experimental work of the writer, which will be published later.

From the standpoint of etiology, pericardial adhesions seem to fall into three classes: (1) The tuberculous which we do not desire to discuss; (2) those resulting from an attack of acute pericarditis or more probably pancarditis secondary to or complicating some acute infectious disease as rheumatic fever, tonsillitis, lobar pneumonia, typhoid, etc. Here the acute pericarditis may or may not result in an effusion. Following this acute stage there usually develop fibrous adhesions, not only within the pericardial cavity, but, more important, adhesions between the pericardium and the anterior chest wall, the pleura, diaphragm or the structures within the mediastinum. This class is the one most easily recognized clinically, not only because of the extent but the nature and location of the adhesion.

The third class includes those cases which give no history of previous acute infections of any kind. This class present adhesions of all grades, mild, moderate or extensive. The adhesions being located at various places within the pericardium and uniting the pericardium with various extrapericardial structures. At times the adhesions are of no clinical importance while at other times they assume a position of immense importance because of the associated cardiac insufficiency and because of the prognosis of certain acute infections in patients suffering with this cardiac insufficiency. The adhesions in this class are probably the result of long and continued injury to the pericardium from chronic infections or some unknown intoxication. In this class we see most typically the associated chronic changes in the liver and kidneys.

In general, this class presents clinical symptoms and physical findings leading to a suspicion or diagnosis of adherent pericardium at a later age than the foregoing class, because the foregoing class is the result of acute infections usually acquired in childhood or early adult life and the cardiac symptoms appear a few years later. The formation of the adhesions in class three is insidious, resulting in cardiac symptoms years later. Unless the adhesions are selectively located, or else are very extensive, the clinical recognition is not only impossible but unimportant. When the adhesions are so placed as to interfere gravely with the cardiac function or are extensive the clinical recognition is important because of the cardiac insufficiency and because of the influence of this insufficiency upon the prognosis of certain acute infections, notably pneumonia and typhoid fever.

The signs present in any case of adherent pericardium will depend upon the efficiency of the heart toward maintaining a normal circulation and upon the location of the adhesions.

For the purpose of a concise delineation of the signs which may possibly lead to a recognition of this pathological state, we may resort to the classical rescription of the signs recognizable by inspection, palpation, percussion and auscultation.

Inspection: A patient suffering with adherent pericardium which has so disarranged the cardiac efficiency as to produce symptoms, presents about the same general symptoms as are common to all cases of cardiac decompensation.

In addition to these general symptoms we frequently are able to see the veins of the neck and face especially full during inspiration, while during expiration the veins collapse. The sign first described by Friedreich was supposed to be of some value in the diagnosis of pericardial adhesions. It is present, however, wherever there is a weakness of the right heart from any cause. Probably the most valuable sign to be noted upon inspection is a distinct retraction of the lower end of the sternum and the costal cartilages synchronous with cardiac systole. This results from adhesions between either ventricle and the pericardium at or near the attachment of the latter to the diaphragm. The retractions will be more distinct upon the side corresponding to the ventricle most densely adhered. The retractions will also be greater if in addition to the ventriculopericardial adhesions there are present phrenopericardial adhesions obliterating the normal phrenopericardial angle. At times these extrapericardial adhesions can be definitely demonstrated by carefully taken stereoscopic plates. The retraction of the costal arch may extend posteriorly to the eleventh or twelfth rib. There should, as Broadbent has observed, be a definite retraction of the costal arches and not merely of the interspaces, as a recession of the interspaces alone may be due to atmospheric pressure associated with extensive cardiac hypertrophy. When there are adhesions between the pericardium and the parietal pleura associated with obliteration of the pericardial cavity adjacent to either ventricle there will be seen systolic retractions of the costal cartilages or interspaces overlying the heart. Upon several occasions the writer has seen the sternum, costal arches and interspaces under prominent systolic retractions where there existed extensive pericardial and extrapericardial adhesions.

A retraction of the interspaces alone over the precordium is frequently seen to result from extensive cardiac hypertrophy; the retractions being near the sternum in right ventricular hypertrophy, and at or near the apex when the hypertrophy is of the left ventricle. Unless borne in mind these retractions might be considered as indicative of pleuropericardial adhesions.

In the study of this series, palpation was of only limited value. The diastolic shock so frequently described over the precordium was absent in a great majority of the cases. When present and distinct it may indicate the presence of rather dense adhesions

about the roots of the great vessels. Of more value apparently is an otherwise unexplainable absence of the impulse, or in the presence of a palpable apex impulse the failure of this impulse to change position corresponding with the change in the position of the body.

Anyone devoting close study to the physical phenomena of pericardial adhesions, surely is impressed with the value of carefully conducted percussion in the clinical recognition of these cases. The left border of cardiac dulness normally changes about 3 cm. with the change from the right-lateral to the left-lateral position. Likewise there is a change of 3 cm. in the lung border over the precordium during deep respiration. If either of these normal phenomena is absent, and its absence not explained by some extrapericardial condition, it remains a strong indication of pericardial adhesions. An absence of a change in the position of the cardiac dulness is present even without extrapericardial adhesions, while the fixation of the lung borders occurs only in the presence of pleuropericardial adhesions.

Auscultation reveals nothing distinctive of adherent pericardium. There may be various murmurs indicating the presence of an associated valvular disease, possibly the result of an inflammatory process responsible also for the pericardial adhesions, meaning, of course, that there existed at one time a pancarditis. This is usually the result of acute rheumatic infection.

The presystolic rumble and reduplication of the first sound are in no way distinctive. There remain certain accessory signs, some of which are present in certain cases, and while not absolutely diagnostic, are of great corroborative value.

Cooper's paradoxical respiratory ratio is of distinct value, but being present also in other conditions, it is only of great assistance if pronounced.

Riess's gastric sounds, whereby the heart sounds assume a loud and metallic quality, when heard over the epigastrium are apparently present when the adhesions are very extensive and involve the diaphragm.

There has been a syndrome described by Pick which today bears his as well as numerous other names, whereby there is chronic pericardial adhesions, chronic mediastinitis, capsular cirrhosis of the liver and chronic peritonitis with ascites. This syndrome has been considered by some as originating in the pericardium and because of the adhesions involving the inferior vena cava produce a passive congestion of the liver and other organs, and in this way account for the abdominal pathology. The pericardial, hepatic and peritoneal findings are quite probably independent and distinct, but the result of a common etiology as a chronic infection or intoxication. Most probably Pick's syndrome is nothing more than a very advanced type of adherent pericarditis described under class 3, the pathology being very extensive and pronounced.

In the diagnosis of adherent pericarditis most probably the greatest assistance comes from the recognition of well-defined cardiac decompensation, wherein there are no demonstrable valvular or myocardial changes to account for the decompensation. This should always arouse the suspicion of adherent pericarditis. Likewise a decompensating heart which reveals no abnormal findings relative to its size, shape and position should be investigated thoroughly for adhesions. Most probably if the physical examination as delineated above is conducted carefully, while bearing in mind the possibility of adherent pericardium, very few cases of extensive adhesions will be overlooked. I believe we have been able in some cases, especially when the adhesions obliterate the cardiophrenic angles or become dense in the mediastinum, to decide the diagnosis by means of carefully taken stereographic plates. When the adhesions are mild or moderate and not selectively located the diagnosis most probably is not only impossible but unimportant.

EFFECT OF THERAPEUTIC DOSES OF MERCURY ON THE KIDNEYS AND THE DURATION OF ITS EXCRETION.

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The renal excretion of the mercurials, following their various methods of internal administration, has been the subject of frequent study in the past. Following their elaboration of a "New and More Delicate Test for the Detection of Mercury," Wile and Elliott were able to add materially to our knowledge of the drug's action, following its use in the form of injection and inunction. It has seemed, therefore, that a similar study of calomel following its internal administration might prove worthy of description. The scope of the experiment, as undertaken at this time, was limited to a calculation of the period of time over which the drug was excreted and a study of its action upon the kidney as determined by urinary findings.

The method for the detection of mercury employed in the experiment, in brief, embodies the use of copper dust in an acid solution of the suspected material. The mercury is taken up to the last trace by the copper dust. The latter is then collected, dried and heated in the distal end of a bulb tube. The mercury is thus vaporized and deposited as an amalgam in a small particle of gold leaf. By this method one-millionth of a grain of mercury in solution can be detected microscopically.

It was interesting to note that in establishing controls for the experiment many patients were found unsuitable for the reason that

they were not mercury-free. Inquiry revealed that the majority of these patients had received previous antisyphilitic treatment, entailing the use of mercury in one of its various forms. In the light of previous studies it is a well-known fact that mercury can be found for years in the urine of patients who have previously received the drug, so this finding was to be expected. Obviously these patients were rejected at once. Controls, finally, were selected from other clinics, each according to the following conditions: (1) Those that gave no history of previous mercurial ingestion must give one negative test for mercury in the urine; (2) if there were a history of previous mercury ingestion or if the patient had ever been exposed to mercurial vapors two successive negative tests over twenty-four-hour specimens were required.

In addition, each specimen of urine was subjected to a complete analysis to ascertain whether it was normal in other respects. Chemical and microscopic tests on a centrifuged specimen were required to be negative. A complete record of all analyses was preserved.

Having thus determined the standards the first application of the test was begun by the internal administration of calomel in the usual way: One-quarter-grain doses over fifteen-minute intervals. The conditions under which the experiment was made were: (1) No drastic saline or other purge should follow the ingestion of the mercury; (2) all specimens must be collected in mercury-free containers at various intervals; (3) only one course of the drug should be given. The various dosages that are most commonly given, therapeutically, were used in the experiment. The urines were then collected at the intervals shown in the tables and were subjected to the test for mercury as described above. The results were carefully tabulated.

SERIES I.—CALOMEL, GRAINS TWO IN ONE-QUARTER-GRAIN (DIVIDED) DOSES AT FIFTEEN-MINUTE INTERVALS.

Patient.	6-hour.	12-hour.	24-hour.	2d day.	3d day.	4th day.	5th day.	6th day.
1	–	–	X	X	X	X	–	–
2	–	X	X	X	X	X	Patient left hospital	0
3	–	–	X	X	X	X	X–	–
4	–	X	X	X	X	X	X	X
5	X	X	X	X	X (X)	X (X)	–	–
6	–	X	X	X	X	X	–	–
7	–	–	X	X	X	X	–	–
8	X–	–	X	X	–	–	–	–

SERIES II.—CALOMEL, GRAINS ONE AND A HALF IN ONE-QUARTER-GRAIN (DIVIDED) DOSES AS ABOVE.

Patient.	6-hour.	12-hour.	24-hour.	2d day.	3d day.	4th day.	5th day.	6th day.
1	–	–	–	X	X	X–	–	–
2	–	–	X	X	X	X	X	–
3	–	X	X	X	X (X)	–	–	–
4	–	–	X	X	X	X	–	–
5	–	X	X	X	X	–	–	–
6	X–	X	X	X	–	–	–	–
7	–	X	X	X	X	–	–	–

SERIES III.—CALOMEL, GRAIN ONE IN ONE-QUARTER-GRAIN DOSES AS ABOVE.

Patient.	6-hour.	12-hour.	24-hour.	2d day.	3d day.	4th day.	5th day.	6th day.
1	–	X	X	X	X	X	–	–
2	–	X	X	X	–	–	–	–
3	–	X–	–	X	–	–	–	–
4	–	X	X	X	–	–	–	–
5	–	X–	X	X	–	–	–	–

SERIES IV.—CALOMEL, GRAIN ONE-QUARTER, ONE-QUARTER-GRAIN DOSES.

Patient.	6-hour.	12-hour.	24-hour.	2d day.	3d day.	4th day.	5th day.	6th day.
1	–	X	X	X	–	–	–	–
2	–	X	X	X	X	–	–	–
3	–	X	X	X	X–	–	–	–
4	–	X	X	X	–	–	–	–

X = Urine showed hyaline casts and trace of albumin.

From these charts it can be seen that:

1. All cases showed a positive test for mercury on the second day.

2. There was a greater excretion of the drug on the second day than any other day.

3. The heaviest excretion of mercury was between the forty-second and the seventy-second hours.

4. Mercury was detected in some cases as early as the sixth hour and as late as the sixth day.

In addition to carrying out the method for detecting mercury in infinitesimal amounts in each urine, every specimen was carefully subjected to both chemical and microscopic tests for the presence of material that might suggest kidney changes. In all cases except those marked X the urine analysis was entirely negative. In the instances marked a trace of albumin and a few hyaline casts were found.

CONCLUSIONS. 1. The excretion of calomel in ordinary therapeutic doses begins within six to twelve hours and is continued until the sixth day, depending upon the size of the dose.

2. A small dose of the drug is excreted as rapidly as a larger dose, but over a shorter period of time.

3. In so far as could be determined by the urine analysis the drug is excreted without injurious effects upon the kidney.

I wish to thank Dr. Udo J. Wile for his invaluable criticisms and for checking over my results, as well as for the laboratory facilities which he placed at my disposal.

REVIEWS

THE MEDICAL ASPECTS OF MUSTARD-GAS POISONING. By ALDRED SCOTT WARTHIN, PH.D., M.D., Professor of Pathology and Director of the Pathological Laboratories of the University of Michigan, Ann Arbor, Michigan, and CARL VERNON WELLER, M.S., M.D., Assistant Professor of Pathology, University of Michigan, Ann Arbor, Michigan. Pp. 267; 156 original illustrations. St. Louis: C. V. Mosby Company.

DR. WARTHIN'S and Dr. Weller's monograph on *Mustard-gas Poisoning* represents a war research problem which was carried on very intensely during the period of the war. It represents an extremely complete and careful study of the medical aspects of gassing and various lesions produced by this gas and the treatment which should be employed in gassed patients. From an experimental and pathological standpoint the book is extremely complete. From a clinical standpoint, however, the book does not represent by any means a complete exposition of the subject. To those who are interested in the clinical aspect of gassing, the regimental and the base hospital surgeon, the particular applicability of the experimental work to the practical is not sufficiently dwelt upon. This applies particularly to the treatment of the pulmonary complications and lesions, and more especially the late results.

Those who have seen large numbers of cases of mustard-gas poisoning have found that the important outstanding lesions were in the skin and respiratory tract. The treatment of the skin lesions as outlined, seems entirely adequate; that of the respiratory tract is not so. Eye lesions were comparatively rare and only infrequently of much importance. Under eye injuries there is recommended the wearing of antidimming goggles. This suggestion is contrary to the advice of the ophthalmologists in the A. E. F. Dr. Warthin also reports a leukocytosis in gas cases, whereas Krumbhaar found that a leukopenia was quite constant, reaching its greatest intensity in the severe cases.

The monograph on this subject represents a really splendid piece of work. The slight criticism that has been expressed by no means reflects upon the excellence of the work. The authors' contribution to the study of this subject is a valuable addition to our knowledge of the effects of mustard-gas poisoning, and it will undoubtedly remain the authority on this subject for many years.

J. H. M., JR.

FACIAL NEURALGIA AND ITS TREATMENT. By J. HUTCHINSON, F.R.C.S., Surgeon to the London Hospital; Examiner in Surgery and late Hunterian Professor at the Royal College of Surgeons. Pp. 216; 37 figures. New York: William Wood & Co.

THIS book, the first in the language, deals with the various phases of trigeminal neuralgia, its types, etiology, pathology and treatment. To the author thanks are due for defining clearly the minor from the major form, two distinct diseases. To the major or epileptiform neuralgia, or "tic douloureux," the volume is chiefly devoted. Prevalent ignorance of the existence of a sure cure for the pain or the unfounded (unless from early statistics) belief that the operation will either kill or cause the loss of sight are largely responsible for the long abject misery of these patients, their frequent addiction to morphin and then to suicide.

The author laments the great delays these patients suffer before being brought for radical operation, the vicious extraction of sound teeth and miscellaneous, useless efforts to find a focus of infection, the employment of drugs (for true major neuralgia is related neither to syphilis, gout nor the rheumatic diathesis; in fact, its etiology is wholly unknown and spontaneous cure is unheard of); ligation of the common carotid artery, excision of the superior cervical ganglion or any of the peripheral operations, all of which are now obsolete. There are only two legitimate procedures: alcoholic injections of the main divisions or of the ganglion, which afford relief for about nine months, and operation on the Gasserian ganglion or its sensory root, which offers permanent cure.

The development of the major operation is traced, chief attention being paid to excision of the ganglion, but particularly to the author's operation, which removes only the outer two-thirds of the ganglion, leaving intact the ophthalmic division and its share of the ganglion, thereby preventing corneal ulceration and lessening the danger of wounding the cavernous sinus. It is unfortunate that Mr. Hutchinson has not acquainted himself more accurately with the American literature in recent years. He states (page 118) that the Spiller-Frazier operation is "more difficult, dangerous and uncertain" than his own method. As to danger, Hutchinson, 70 cases, 3 deaths, 4 per cent. mortality; Frazier, 129 cases, 1 death, 0.77 per cent. mortality. The rankest injustice to Americans is the publication of a full-page illustration (including the legend) of a woman with a depressed zygoma, an ugly, disfiguring scar on the temple and her eyelids on one side sewed together for corneal ulceration. The legend, in part, reads: "Showing site of flap incision for the Spiller-Frazier operation." He goes on to say that these are "the conditions which should be avoided." Frazier never resects the zygoma or cuts outside the hair

line. Lastly, Hutchinson refers to Cushing as doing an obsolete, complicated operation, which has removal of the ganglion as its goal, whereas he actually performs the Spiller-Frazier operation, which leaves the ganglion intact. J. A.

ANAPHYLAXIS AND ANTI-ANAPHYLAXIS. By A. BESREDKA, Professor at the Pasteur Institute. English Edition by S. ROODHOUSE GLOYNE, M.D. (Leeds), D.P.H. (London), Pathologist to City of London Hospital for Diseases of the Chest, Victoria Park. Pp. 143. St. Louis: C. V. Mosby Company.

THE translation of this monograph has been undertaken for the purpose of presenting to the English-speaking public the work of Besredka on the subject of anaphylaxis which he had accomplished before the war started. The book is introduced to the reader by four different introductions, following which is a historical sketch of anaphylaxis. The three succeeding chapters dwell on the sensitizing injection, the toxic injection and the anti-anaphylactic (desensitization) injection. The next two chapters are on anaphylaxis in the presence of other substances, and theories relating to anaphylaxis. The last chapter is a summary by the translator of the recent work on anaphylaxis. This last chapter is by no means complete, nor can the translator be blamed entirely for that on account of the disruption of the mail service, publication, etc., during the war or immediately following it.

Besredka undoubtedly stands as the great authority on the subject of anaphylaxis. He believes that the phenomenon of anaphylaxis is produced by an antibody becoming attached to nerve cells, permitting the entrance of the antigen which suddenly penetrates them and producing the characteristic symptoms. He believes that there is no true anaphylatoxin.

The monograph presents the subject in a clear, precise manner. It will be of particular value to those who are interested in this subject, more especially to those who are giving therapeutic sera and vaccines. J. H. M., JR.

SYPHILIS. By HENRY H. HAZEN, A.B., M.D., Georgetown University. First Edition. Pp. 647; 160 illustrations (16 in color). St. Louis: C. V. Mosby Company.

IT is the greatest pleasure to read a book that raises the subject of syphilis above the level of a chapter in genito-urinary diseases and places it on the wonderful medicine-wide plane to which it is entitled. This Dr. Hazen's book does, for he brings to us not only his own

well-known efforts in this field, but has collaborating with him such authorities as Major M. A. Reasoner on infection and immunity, Dr. John E. Lind on nervous system involvement, Colonel C. F. Craig on the Wassermann test, and Dr. Jay F. Schamberg on the arsenical preparations. Dr. Virginius Dabney and Dr. L. H. Greene have written on the ear and eye infection respectively. Dr. H. A. Fowler's contribution on syphilitic nephritis is a most important exposition, while the chapter on endocrine gland infection is a valuable addition, with probably the first correlation of this literature. It is a pity that under prophylaxis the author did not make the effort to incorporate the wonderful lesson the American Army taught in France, and one might likewise criticize the chapter on diagnosis as putting too much dependence on the Wassermann test, or, possibly better said, by omitting the exposition of the clinical diagnosis. The chapter on treatment leaves one thoroughly familiar with the various drugs at hand and their individual administration, but lacks the proper guide and exact advice as to when and how to use them. The book is written throughout in a uniform, easy style that is most readable and loses none of this charm under the handling of the various authors. Dr. Hazen has a most happy ability in introducing quotations from other writers, and strengthens his subject repeatedly by using in a most admirable way the teachings of other authorities that leaves with the reader the feeling that the ground has been completely covered and the last word has been said. The book is profusely and splendidly illustrated; it is published in a way that leaves nothing to be asked, and one of its most valuable adjuncts is the excellent bibliography that is appended to each chapter. A. R.

Diseases of the Ear, Nose and Throat. By Herbert Tilley, Surgeon to the Ear and Throat Department, University College Hospital, London. Fourth edition. Pp. 844; 74 illustrations. London: H. K. Lewis & Co., Ltd.

This work, as it now appears in its fourth edition, is a very complete and excellent text-book on diseases of the nose and throat. Since the last edition, as the author states in his preface, so great an advance has been made in certain phases of rhinology and laryngology that it has been necessary to absolutely rewrite the chapters on frontal sinus suppuration, the technic of enucleation of the tonsils and the subject of endoscopy, and to add entirely new chapters on certain affections of the trachea and esophagus, intranasal operations on the lacrimal apparatus and the intranasal routes for operations on pituitary tumors.

On the whole the book gives one the impression of being based more on the author's great experience than on a searching review of

the world's literature, and while this in some ways gives the book a peculiar value, we believe that a larger use of the literature outside of his own country would make an international adoption of the book much more easy. In this connection it is interesting to note that the author describes very closely what we in this country are in the habit of calling the Sluder method of removing tonsils, and gives Drs. Whillis and Phybus, of Newcastle-upon-Tyne, the full credit of devising the operation. Likewise an almost identical instrument with the Laforce tonsillectome is called Elphick's guillotine. Very frequently we note with pleasure a very extensive and accurate knowledge of pathology and modern laboratory revelations, and though this showing is not consistent throughout the book, the laboratory aspect is fairly reliable; much more so than the average book on diseases of the nose and throat. The clinical and operative side is excellent, well illustrated and with clear, easily read text, and the number of both minor and major operations carefully described is quite amazing. The great value of the work lies in the thoroughness with which the author has covered his field, not skimping any part, but giving space enough to all subjects for sufficient detail to make the work a real text-book of the whole category of nose and throat ailments. G. B. W.

ANATOMICAL DIAGRAMS. FOR THE USE OF ART STUDENTS. By JAMES M. DUNLOP, A.R.C.A., Lecturer on Artistic Anatomy in the Glasgow School of Art. Fourth edition. Pp. 72; illustrations on each page. New York: The Macmillan Company.

BY the use of colored diagram the author presents the osteology and myology of the human body. The aims are to show the part played by the skeleton in determining the external form and to illustrate the shape and arrangement of the various muscles, especially the subcutaneous ones. The fact that this is the fourth edition shows that art students find it useful in the studio.

W. H. F. A.

A LABORATORY OUTLINE OF EMBRYOLOGY, WITH SPECIAL REFERENCE TO THE CHICK AND THE PIG. By FRANK R. LILLIE, Professor of Embryology in the University of Chicago, and CARL R. MOORE, Instructor in Zoölogy in the University of Chicago. Revised edition. Pp. 66. Chicago: University of Chicago Press.

THIS is a small book in paper covers, containing directions for laboratory work in embryology as given to medical students in the university of Chicago. For over fifteen years this book with

various alterations, has been utilized continuously in classes, and the present form therefore represents a well-tried and standard course of instruction. In the experience of the authors it has been found preferable for the student to follow out the development of each organ-system separately, through several ages of embryos, than to study each stage of the embryo in its entirety.

W. H. F. A.

BACTERIOLOGY IN ABSTRACT. By A. B. WALLGREN, B.S., M.D., Assistant Professor of Biology, University of Pittsburgh. Second edition. Pp. 338. Pittsburgh, Pa.: Medical Abstract Publishing Co.

THE second edition of bacteriology in abstract has recently appeared. The amount of useful and helpful knowledge contained in so small a volume is surprising. All fields that larger textbooks deal with are gone into here; necessarily, of course, in only an outlined, sketchy way. The index is fairly complete. The book is all and more than its author claims for it, and should prove a very useful volume for the student. H. F.

DISEASES OF CHILDREN. By JAMES BURNET, M.D., M.R.C.P. (Edin.), Physician for Diseases of Infancy to and Physician in Charge of the Welfare Clinic at the Marshall Street Dispensary, Edinburgh. Second edition. Pp. 416; 9 illustrations. Edinburgh: E. & S. Livingstone. New York: William Wood & Co.

ARRANGEMENT of chapters in this small volume differs somewhat from the usual custom followed in pediatric works. In the first two chapters the examination of sick children and points of difference between children and adults are briefly but well described. Next in order are diseases of the newborn. After a chapter on diseases of the respiratory system and one dealing with diseases of the circulatory system, infant-feeding occupies a number of pages. Here the author discusses only his personal beliefs. Contrary to most authorities he does not advocate the use of sugar as an addition to milk mixtures, nor does he think that barley water is an advantage. He states that it is a fallacy to suppose that infants lose weight if sugar is omitted. Briefly, then, when it is necessary to feed babies artificially he uses only dilution of cows' milk with water. Citrated whole milk has given him good results, and scalded milk he finds preferable to raw, sterilized or pasteurized milk. While this chapter makes interesting reading, it does not seem to the reviewer that it

can be strongly recommended to the student or general practitioner as a system of procedure. Space does not allow of further analysis. Suffice it then to say that the usual chapters on various subjects are to be found. These are necessarily brief, due to the small size of the book. A. G. M.

THE AFTER-TREATMENT OF SURGICAL PATIENTS. By WILLARD BARTLETT, A.M., M.D., F.A.C.S., and Collaborators. Two Volumes. Pp. 1066; 434 original illustrations. St. Louis: C. V. Mosby Company, 1920.

THESE volumes are certain of a hearty welcome from English-speaking surgeons. Throughout they have two properties of singular merit: they are essentially practical and they are up to the minute. As to the little details of postoperative management, most surgeons, even in the larger cities, allow themselves to practice for all cases one or two methods of treatment that may have seemed to prove of magic value in some "prize" case or other; in minor conditions they are prone to neglect the experience of others and the set-back to intercommunication of ideas during the war has accentuated this. To offset it and to strengthen the foundation for the rational, effective cure of the surgical patient a systematic reading of this work, embracing the experience of a group of able surgeons who have drawn generously from the literature of America, England, France and the German-speaking countries is particularly timely and necessary. Necessary because such a reading cannot but impress the reader with the host of modern methods that simplify convalescence, add untold blessings to the comfort of the patient and not infrequently in themsleves effect cure or save life, methods that have not yet entered widely into circulation or at least too vaguely to be heeded, or perhaps old methods undeservedly forgotten.

Much is devoted to the minor subjects: postoperative subjective symptoms, sleeplessness, hiccough, headache, backache, skin eruptions, urinary retention, feeding, etc. There are valuable chapters on shock, miscellaneous abdominal tragedies, the various postoperative infections, the treatment of wounds, two unusually suggestive chapters on massage, exercise and physicotherapy and a chapter on radium and roentgen rays in malignancy, which is deserving of the closest study. The follow-up idea is represented by an able chapter on the reconstruction of the patient and by a series of forms prepared by Stuart McGuire for the guidance of patients leaving his immediate care.

It is a work that includes the widest variety of subject-matter, much too wide for mention, and is a book for the hospital intern and surgeon rather than for the student of medicine.

With the exception of two or three contributors it is a product entirely of St. Louis men. Much of the first volume, which deals with general considerations, was written by O. F. McKittrick, and most of the second, dealing with regional surgery, by Williard G. Bartlett. The printing is good, the illustrations unusually pertinent and the index a real service. J. A. D.

PHYSICAL RECONSTRUCTION AND ORTHOPEDICS. By HARRY E. STEWART, M.D., Capt., Medical Corps, U. S. A., Division of Orthopedics; Attending Surgeon, New Haven Orthopedic Dispensary; Instructor in Medical and Orthopedic Gymnastics and Massage, New Haven Normal School of Gymnastics, etc. Pp. 240; 69 illustrations. New York: Paul B. Hoeber, 1920.

IT has been the author's object to present in condensed form the main principles of orthopedics in the treatment of defects in childhood, war injuries and industrial accidents, laying stress upon the treatment by massage, exercise, physical, mechanical and electrical and other types of physicotherapy.

The methods advocated have been tried out and proved of advantage in the reconstruction of the wounded of our own and allied nations, and are adaptable to our civil and industrial problems of like nature.

The problems of exercise, baking, massage, vocational therapy, electrotherapy and hydrotherapy are discussed in detail.

The application of these various treatments for congenital defects, spinal curvatures, joint injuries and diseases, foot-strain, fractures and dislocations is described in detail also.

The work should be of great value to physicians, reconstruction aides, physical directors, orthopedic assistants and nurses, not only in the better understanding of their work, but in emphasizing the vital importance of this so long neglected field. E. L. E.

MEDICAL CLINICS OF NORTH AMERICA. Mayo Clinic Number, Volume III, No. 3, 1919. Boston Number, Volume III, No. 4, January, 1920. Philadelphia and London: W. B. Saunders Company, 1920.

THE Mayo Clinic number of this bi-monthly publication has an unusually large number of contributors, twenty-three of whom present some communication on medical or closely allied subjects. The majority of these are reports of cases which are used as a text

for a brief discussion of the subject suggested by the case. There is a certain uniform excellence about these papers, and it would hardly seem fair to pick out any for a special commendation or criticism. As one of the articles is by Dr. Kendall, a chemist and not a physician, it will not be unjust to the other contributors to say that it is especially interesting, recounting, as it does, the end results of the splendid research which has been carried out by him and by his collaborators on the thyroid gland at the Mayo Clinic in the last ten years.

The Boston number of the *Medical Clinics* contains seventeen contributions from members of the teaching staff of Harvatd University. These articles are all very interesting and well wort h critical reading and study. The articles of the Harvard men exhibit the best type of medicalwork and represent impressively the purpose for which these *Clinics* are published. They give authors an opportunity to describe unusual cases or to writs on subjects which are for the most part protean, and yet which are matters that the average reader frequently does not have at his finger-tips and which it is to his decided advantage to review from time to time. Furthermore, they present the newer diagnostic methods, therapeutic progress and the recent advances in general in the studies of the conditions which the author is describing.

J. H. M., Jr.

Surgical Clinics of Chicago. Bi-monthly Volume IV, No. 1. Pp. 231; 83 illustrations. Philadelphia and London: W. B. Saunders Company, 1920.

This number of the *Clinics* well sustains the reputation held by this work in the past. The contributors are all in the foremost rank in their respective branches and have many times presented articles to the readers of medical or rather surgical literature.

Each article is a text in itself and invariably illustrates some important point in diagnosis or some novel, useful and essential list of surgical technic.

The great value acquired from the *Clinics* is due to the concrete knowledge obtained from the individual patient explained before you. The problem is presented and solved before the reader's eyes.

E. L. E.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Origin and Nature of Multiple Sclerosis.—MARINESCO (*Rev. Neurol.*, 1919, xxvi, 481) thinks multiple sclerosis should be investigated as an inflammatory process caused by an infectious agent. The lesions are inflammatory in character and the sclerosis is secondary. A *resume* of previous experimental work is given. The author injected the spinal fluid from two cases of multiple sclerosis into guinea-pigs by intraspinal, intracerebral and intraperitoneal routes. The two pigs which had had intracerebral injections showed motor difficulties. The fluid from their fourth ventricles contained spirochetes, unlike the treponema of syphilis. The work was not carried further.

An Interesting Spinal Syndrome Following Gunshot Wounds.—LITTIG (*Monatschr. f. Psychiat. u. Neurol.*, 1919, xlvi, 112) reports nine instances of a spinal-cord syndrome named by him monoplegia spinalis spastica superior. Briefly this consists of a high cervical cord lesion followed by a spastic paresis or paralysis of one arm. Occasionally there are sensory disturbances in the region of the ulnar side of the paretic arm. This syndrome is usually the end-result of many cord wounds, such as a diplegia, hemiplegia or Brown-Séquard symptom complex, but may be primary.

Renal Glycosuria.—ALLEN, WISHART and SMITH (*Arch. Int. Med.*, 1919, xxiv, 523) found three cases of renal diabetes among forty supposed diabetics at U. S. G. H. No. 9. The histories and detailed reports of the laboratory tests are given in the article. No instances of levulose,

pentose or glycuronic acid excretion were encountered. No clue as to etiology was found. The prognosis seems to be good, for in no case in the literature has injury resulted from the anomaly, and it has never been known to have ceased. In the instances reported sugar excretion and water excretion have behaved as independent functions. Increase of sugar output did not increase water output. The salient features of carbohydrate metabolism in the three cases and in nearly all of the genuine cases are: "(1) A tendency to glycosuria so strong that sugar freedom is possible only with stringent restriction of diet or actual fasting to such a degree that health would be seriously impaired by attempting to keep glycosuria absent, if, indeed, life were possible at all—the cases in this respect surpassing true diabetes except for very rare examples of extreme severity; (2) normal power of actual carbohydrate utilization, as manifested by 'paradoxical tolerance;' *i. e.*, though some process in the kidney or elsewhere causes the waste of a certain quantity of carbohydrate, and this quantity may increase with increased carbohydrate ingestion, yet the soundness of the assimilative function is shown by the ready utilization of the greater part of every starch or sugar intake, no matter how large; (3) though the blood-sugar level is subject to some variations the low values found in many cases, even after large starch or sugar ingestion, stand in contrast not only to the condition in diabetes but also to the hyperglycemia of normal persons after such feeding." The authors lay emphasis on the desirability of ascertaining in each instance the nature of the reducing substance present in the urine obtained as soon as possible after leaving the kidney.

Exophthalmic Goitre, Basal Metabolism In. — MEANS and AUB (*Arch. Int. Med.*, 1919, xxiv, 638) have followed many patients with exophalthalmic goitres over several years and have been able to observe the results of various forms of treatment. The method of approaching the results is based on the study of the basal metabolism. Short abstracts of the clinical findings of the hyperthyroid patients are included. The other data are presented by tables. Patients with exophthalmic goitre were treated either by rest alone, quinine hydrobromide, roentgen ray or operation or by a combination of these methods. They conclude that "using the basal metabolism as an index of toxicity in exophthalmic goitre" the majority of patients show as good results after two or three years following roentgen-ray treatment as following surgical treatment. "The safest program for the treatment of exophthalmic goitre, as a whole, is the routine irradiation of thyroid and thymus glands, in all cases, with surgery held in reserve for patients who do not then do well. Surgery is contra-indicated with patients whose metabolism is rising in spite of complete rest in bed, and also in patients of the type with moderate tachycardia and great metabolism increase, except when they have previously had thyroid and thymus glands treated by roentgen ray." They also believe that basal metabolism determinations may be of differential diagnostic importance in certain border-line cases.

Entameba Histolytica, Report on the Treatment of; Infections.— GUNN and SAVAGE (*Jour. Royal Army Med. Corps*, London, 1919, xxxiii, 418) report the result of treatment in 383 cases at Alexandria.

The diagnosis was based on the presence of entameba histolytica in stools. The patients were in every stage of the disease, some being only cyst carriers, some having large tender livers with high fever. They recommend that acute cases be treated with 1 grain of emetine daily for twelve days, followed by 3 grains of emetin and bismuth iodide for fourteen days. If the condition is very severe when treatment is first begun, and may probably prove fatal if not rapidly brought under control, they recommend an intensive course of treatment of 1 grain emetin hypodermically daily in the morning and 2 or 3 grains of emetin-bismuth-iodide at night. The patient should be carefully watched while such large doses are being administered.

Lumbar Puncture in Brain and Subdural Abscess.—Barries (*Arch. f. Ohren, Nasen. u. Kehlsop f. h.*, 1919, civ, 66) discussess at length the cerebrospinal fluid changes in brain and subdural abscesses. These may be placed in four groups as follows: (1) The fluid is entirely negative in uncomplicated brain or subdural abscess and may remain so until death. (2) The fluid may be cloudy but sterile, later becoming cell-free, in instances showing minimal leptomeningitis. (3) The fluid may be cloudy and contain bacteria, later becoming sterile if there is an extensive leptomeningitis. (4) The fluid may be cloudy and contain bacteria in cases running the course of an acute purulent meningitis. The fluid obtained by lumbar puncture may be of considerable help in diagnosis and prognosis if examined repeatedly. Since, as shown in the groups above, favorable changes are common in the fluid as the disease progresses, a single lumbar puncture may give a wrong impression of the extent and gravity of the meningeal involvement. In certain instances the brain abscess proves fatal although the spinal fluid shows changes which the author calls benign. By repeated lumbar punctures it is possible to gain knowledge only of the extent and gravity of the meningeal changes secondary to a brain or subdural abscess.

Spirillosis Following a Traumatic Hemothorax (Spirillose Pleurale au Cours d'un Hemothorax Traumatique).—Lancereaux (*La presse méd.*, 1919, xxvii, 556) observed a soldier, wounded by a small piece of shell at the left base. The foreign body was near the heart and moved with its pulsation. There was a large hemothorax. On the sixth day 1500 c.c. of bloody fluid was removed from the left pleural cavity. The fluid was sterile. Tapped again and in the fluid there were many active spirilla seen by ultramicroscope and stained specimens showed spirilla. The patient recovered after three thoracenteses and 0.15 gm. novarsenobenzol intrapleurally.

Neurological Complications of Typhus (Les Complications Nerveuses du Typhus Exanthématique).—Paulian (*La presse méd.*, 1919, xxvii, 541). After about fourteen days' incubation slight chills occur and malaise, backache, headache and fever appear. The face is flushed. About the fifth day of fever the exanthema appears. Its character may vary, at first discrete, at times petechial or even purpuric. There is no relation between the fever, the exanthem and the clinical form of the disease. Delirium appears early. About the thirteenth day the fever begins to fall and remits completely by the fifteenth day. In the

severe types there is carpologia, the eyes injected, rapid respirations, tachycardia, cyanosis, trismus, stiffness of the neck, Kernig's sign and at times hiccough—a very grave sign. Coma vigil is often present. A meningeal reaction is constant—from the first to the fourth day. Cerebrospinal fluid contains mainly lymphocytes; fourth to twelfth day mononuclears; twelfth to convalescence lymphocytes. Nervous complications of two types: (1) During disease and (2) during convalescence. These are, briefly, hemiplegias, nuclear and midbrain lesions, postfebrile confusional states, regressive cerebellar syndromes, myelitides, neuritis and polyneuritis.

Occurrence, Course and Prevention of Chronic Manganese Poisoning.—EDSALL, WILBUR, DRINKER (*Jour. Industrial Hygiene*, 1919, i, 183). Manganese poisoning occurs among workers handling MnO_2 in manufacture of Cl; in grinding of MnO_2; in mill employees who work in dust containing Mn as oxides and silicates. Diagnostic points are: exposure for three months; languor and drowsiness; expressionless face; monotonous voice; muscular twitching—fine or very gross—cramps and stiffness in calves; worse at night or after exertion; hyperreflexia; ankle and patellar clonus; retropulsion and propulsion; slopping gait. Sensation intact; urine, blood, cerebrospinal fluid; sphincters normal. After harm is done there is no treatment. Problem is one of prevention.

Patches of Deep Pigmentation of the Oral Mucous Membrane not Connected with Addison's Disease.—WEBER (*Quart. Jour. Med.*, 1919, xii, 404) reports a patient, aged fifty-seven years, a Hungarian Hebrew, with remarkable pigmentation of the buccal mucous membrane of the palate and lips. There was no pigmentation of the skin. Necropsy showed extensive miliary tuberculosis without involvement of the pancreas, pituitary or pineal body or either suprarenal. No cause for the pigmentation could be discovered. He concludes: "There is a certain group of cases in which pigmentation, not connected with Addison's disease, occurs in the mucous membrane of the mouth. The pigmentation is in the form of blackish spots and patches in the mucous membrane of the lips or cheeks and sometimes of other parts of the mouth. It is associated with pigmentation of the skin of the face, especially about the mouth and possibly of other parts of the body. It occurs in persons of dark complexion, perhaps especially in Roumanian Jews and in certain races such as Lascars. It is of unknown causation and seems in some cases to be of "physiological" or perhaps of atavistic origin. It may be analogous to the black patches often present in the oral mucous membrane of dogs and other animals. It appears to be allied to simple pigment nevi of the skin on the one hand and to freckles on the other. Jonathan Hutchinson was probably the first to call attention to this class of pigmentation, which perhaps should include various cases published by French authors under the headings "physiological pigmentation" and "racial pigmentation." The author has carefully reviewed the literature of the subject.

Recent Additions to Our Knowledge of Typhus: Acquisitions Récentes sur le Typhus Exanthématique.—FOURCADE (*La presse méd.*,

1919, xxvii, 548). In 1909 Ricketts found oval rods, at times biscuit-shaped, and polar staining in the lice fed on infected blood of humans and monkeys. Prowazek, in 1913, found them in lice in Serbia. In 1916 da Rocha Lima found the same in the gastro-intestinal epithelium of pediculosis vestimenti and called them Rickettsia Prowazeki. The morphology and tinctorial qualities are given in the text. The louse seems to be obligatory intermediate host. The patient can infect the louse only during the febrile period. The louse becomes contagious four days after its infecting repast. The disease can be transmitted to man, apes and guinea-pigs. One attack confers immunity. The reaction of Weil-Felix is of great diagnostic importance. The technic is that of Widal's reaction, using Bacillus proteus X 19 of Weil-Felix instead of the typhoid bacillus. The reaction is positive in 50 per cent. of cases in the third week and constant after defervescence. Often a titer of $\frac{1}{5000}$ is found. A titer of $\frac{1}{50}$ is diagnostic.

SURGERY

UNDER THE CHARGE OF

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The Condition of the Appendix in Five Hundred Laparotomies on Patients Representing No Symptoms of Appendicitis.—Williams and Slater (*Ann. Surg.*, 1919, lxx, 535) report the results of their study of the appendiceal pathology met with in the course of the routine examination of the right iliac fossa during five hundred gynecological operations. About one-third of all women operated on for various pelvic conditions, show undiagnosed lesions of the appendix. In some instances these lesions are the result of extension of an inflammatory process to the appendix from the pelvic organs, but at least one woman in every five shows an appendix lesion without symptoms and without discoverable cause (so far as the pelvic organs are concerned). These lesions are nearly all chronic in nature and consist of the following types: (*a*) adhesions without change in the muscular or mucous coats, (*b*) chronic inflammatory changes in all the layers, (*c*) pericecal veils. The frequency of these lesions is of importance in its relation to two questions: (1) Are such undiagnosed lesions of the appendix the undiscovered cause of reflex symptoms elsewhere? (2) Is there such a clinical entity as chronic appendicitis, or are the symptoms usually ascribed to chronic appendix disease in reality due to some other condition? The writers are inclined to the latter view.

Penetrating Chest Wounds.—Lebowitz and Nadler (*Surg., Gynec. and Obst.*, 1919, xxix, 429) reports the results of 276 penetrating wounds

of the chest admitted to a base hospital in France. The observation of the average case was confined to a period extending from the sixth to the thirtieth day after injury. The mortality of penetrating chest wounds that reached the base was low (5.4 per cent.), due chiefly to sepsis, pocketed empyema, and associated injuries. These patients require treatment in special wards. Coöperation of internist, pathologist, roentgenologist, and surgeon is essential. Hemothorax is the commonest event in chest wounds. Early diagnosis of infection is the most important duty at the base. Thoracotomy for infected hemothorax is the most frequent surgical procedure at the base hospital. The Carrel-Dakin treatment for empyema gives good results. Primary intrathoracic operations with closure may be performed easily after injury, in properly selected cases, with no more danger than abdominal operations. Of 21 cases operated upon and closed, 9 remained sterile.

The Technique of Gall-bladder and Common-duct Surgery.—RICHTER (*Surg., Gynec. and Obst.*, 1919, xxix, 455) says that the technic of gall-tract surgery is in the process of becoming standardized. The cystic duct should be isolated before division to insure the safety of the common duct. In the large acutely distended gall-bladders the cystic duct is pushed backward and upward away from the operator. If in these cases the peritoneum, as it is reflected from the liver on to the gall-bladder, is incised enough to admit a finger, the gall-bladder can be peeled out of its bed. The release of the tense gall-bladder in this way will cause the fundus to push its way out of the incision, and the cystic duct becomes mobilized and more accessible. The cystic duct should, Richter believes, rarely be clamped with its vessels *in toto*. He considers it unnecessary to ligate the cystic duct close to the common duct, but one must avoid the careless ligature of the apex of the gall-bladder. The reflected peritoneal flaps from the gall-bladder should not be sutured over the denuded liver, but should merely be pressed against it. The position of the raw surface is such that massive adhesions to it are naturally objectionable. The gauze pack is a much more patent cause of adhesion than the raw surface *per se*. Andrews suggests dropping the omentum in between the liver and the duodenum as a method of minimizing adhesions. Though many operators close the abdomen without drainage, it is almost universally suggested that drainage should be instituted after cholecystectomy. Willis has reported a series of thirty-eight cholecystectomies with drainage, with one death. This can be done safely without excluding the stump of the cystic duct from the peritoneum. Richter considers it illogical to drain the common duct or leave a tube in it following choledochotomy, provided no obstructive lesion is left behind. It is an essential requirement in carrying out immediate suture that the common duct should be patent; that no stone in the ampulla, no partial closure of its orifice from a thickened muscle of Oddi, or chronic pancreatitis should be present.

A Case of Sarcoma of Stomach.—KOETTLITZ (*Arch. méd., Belg.*, 1919, lxxii, 136) says that sarcoma of the stomach merits especial attention because of the rare occurrence of the disease. The patient, a musician, aged twenty-one years, presented himself for consultation June 24, 1915. He had been suffering for one to two years from vague gastric distress,

which had become exaggerated the last forty days. His father died at fifty-one of probable gastric carcinoma and his grandmother died of the same disease. The sickness began with aqueous regurgitations about one hour after eating. Rarely he had vomiting. He gradually lost weight over a period of two years. There was tumor to the left of and above the umbilicus. There was achylia gastrica, plus a tumor not involving the pylorus or at least not obstructing its action. The patient refused operation for forty-five days. During the period he was under observation he had severe periods of diarrhea. At operation there was found a large inoperable tumor in the pyloric region, involving also the pancreas. There was a chylous ascites present. The pathological report of a nodule was fibrosarcoma. He compares his case with Gosset's compilation in 1912 of 171 cases.

A Case of Strangulated Hernia with Volvulus.—HUGHES (*British Med. Jour.*, October 25, 1919, p. 527) reports a case which is interesting for several reasons: Volvulus occurring in a hernial sac is rare; the symptoms were remarkably mild considering the condition which existed; the patient gave no trouble during convalescence and the wound healed by primary intention despite the offensive nature of the sac contents. The hernia was a left-sided inguinal, which had been present for some months. The strangulation began the day previous. The omentum and bowel in the sac were gangrenous. It was found that the bowel was twisted on itself and that a true volvulus existed. The gangrenous omentum was removed and the gangrenous bowel resected, end-to-end anastomosis being done. The bowel dealt with was the pelvic colon. The patient made an uninterrupted recovery.

Radium in the Treatment of Tuberculous Adenitis.—MOLYNEUX (*British Med. Jour.*, November 29, 1919, p. 705) says that he is convinced that the day of radical operation for tuberculous glands will soon be past. Radium is, if properly used, a safe and, as far as he can see, a certain cure, whether for an early or an advanced case of tuberculous glands. He has treated between twenty and thirty cases during 1913–1914. Unless there were sinuses already present no scars were left. In no case was any ulceration caused. Fifteen milligrams of radium bromide applied on a special applicator for 150 mg. hours is suitable for each group attacked. The patients usually had two applications a week. The treatment is continued until all signs of trouble have disappeared. Three cases illustrating different degrees of the disease which were treated are reported.

The Importance of the Spleen in Resistance to Infection.—MORRIS and BULLOCK (*Ann. Surg.*, 1919, lxx, 513) says that very little experimental evidence to refute or support the widespread impression that the spleen plays a part in resistance to infection has been offered. No experimental work can be entirely trustworthy which does not include the recognition and elimination of outside sources of error. The work of Bardack, Roger, Tizzoni and Cattini, Kourlow and others is reviewed, showing the conflicting opinions on the question. On the whole it cannot be said that the blood changes following splenectomy furnish any positive evidence of an impaired ability on the part of the body to

resist infection, but they may be an indication of increased susceptibility to infection and imperfect reaction against it. Thirty-six splenectomized rats were used together with thirty-six controls. It was observed that the splenectomized animals almost invariably died before the controls when they were exposed to chance laboratory contagion, the death-rate among the splenectomized animals being 80.5 per cent. as compared to 38.9 per cent. in the controls. Their results after numerous carefully controlled experiments show in a very definite manner that while the animals get along fairly well without a spleen in the absence of any infection, the reverse is the case when the organism is put to the strain of resisting acute bacterial invasion. Under the circumstances they infer that the spleen normally aids tremendously in resisting infectious processes in rats, and that its removal temporarily robs the body of its resistance until such a time, at least, as compensatory processes will have a chance to reëstablish this.

THERAPEUTICS

UNDER THE CHARGE OF

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Arterial Hypertension.—ALLEN (*Jour. Am. Med. Assn.*, 1920, lxxiv, 652) deals in this article particularly with the restriction of salt and fluid as therapeutic agents in the treatment of hypertension. He believes that suitable chloride restriction is a great factor in making patients with hypertension more comfortable, diminishing the danger of apoplexy and possibly checking the progressiveness of the disorder. By far the best results are obtained in the earliest cases when the hypertension is intermittent rather than continuous. Early diagnosis, therefore, is important, and Allen hopes that chemical tests, such as for blood chlorides and chloride threshold (the normal values of which are still undecided), may help in the early diagnosis. The practical application of low chloride and diminished fluid intake has certain limitations, which he mentions: (1) A diet reasonably satisfying, and at the same time poor in salt, is a difficult diet to arrange. (2) A certain quantity of salt is considered indispensable in a permanent ration. This is stated as approximately 2 gm. for normal individuals. The limits have not been determined for nephritis patients. The chief untoward effect of salt deprivation is weakness, and it is therefore necessary to work out salt rations for individual nephritic patients. (3) Such restriction of salt or fluid is only palliative, and success is not as universal as, for instance, in the treatment of diabetes.

The Role of Carbohydrates in the Treatment of Toxemia of Early Pregnancy.—TITUS, HOFFMANN and GIVENS (*Jour. Am. Med. Assn.*, 1920, lxxiv, 777) discuss the subject of the treatment of the toxemias of pregnancy. They are convinced, from their clinical experience, that liberal carbohydrate feeding is beneficial in the treatment of this disturbance. Mild cases of nausea and vomiting may be controlled by increasing the carbohydrates of the diet and an avoidance of more than short intervals of fasting by the taking of food more frequently. Increased carbohydrate intake is obtained by giving the patient from 8 to 16 ounces of a 10 per cent. glucose and 2 per cent. sodium bicarbonate solution daily by mouth. More severe cases may require increased quantities of this solution, given both by mouth and by rectum. They give to seriously toxic patients additional carbohydrate, easily utilizable, by intravenous injection of from 15 to 25 gm. of glucose in from 250 to 300 c.c. of water. This is given from one to three times daily. They believe that the intravenous injection of glucose solution is a valuable therapeutic measure, and also that the rate of its absorption and storage by the liver is an index of liver efficiency that is of prognostic value.

Protein Diets and Undernutrition in the Treatment of Diabetes.—ALLEN (*Jour. Am. Med. Assn.*, 1920, lxxiv, 571) states that a possible diet after fasting is one composed wholly or chiefly of protein, and this plan has seemed the most useful for maintaining strength during the period of undernutrition necessary for attaining a normal blood-sugar. Actual suffering from hunger is prevented by the use of materials to furnish bulk (bran, agar, celluflour, "India gum," liquid petrolatum, soups, small quantities of thrice-boiled vegetables), without which such low diets would scarcely be practicable. In some elderly patients slight hyperglycemia and nitroprusside reactions may be permissible to avoid undue hardships, but diabetes after the age of forty is by no means always benign, and not infrequently requires stringent measures to control it, especially after long neglect. The more severe the diabetes and the younger the patient the more rigorously should hyperglycemia and all other symptoms be controlled from the outset. Such a policy often means a considerable reduction of weight and strength as compared with the level which can be maintained temporarily by higher diets, and its justification depends on the belief that patients are best off in the long run when their weakened function is spared as thoroughly as possible.

Treatment of Bronchial Asthma.—GOTTLIEB (*Jour. Am. Med. Assn.*, 1920, lxxiv, 931) discusses the treatment of bronchial asthma from its various standpoints, climatic, specific and drug. He believes that the climatic treatment is only of value in cases of asthma due to anaphylaxis to various pollens and that the beneficial effect is due to removal of the exciting cause. Patients who are anaphylactic to foods are benefited by the elimination of such articles from their diet. Those patients who are sensitive to bacterial proteins alone, or, as frequently occurs, complicated by food anaphylaxis, frequently receive benefit from bacterial vaccines. In case the vaccine treatment subcutaneously has no effect, intravenous injections should be tried. Great care is necessary in the

administration of the proper dose. The author is of the opinion that in about 50 per cent. of the cases of hay-fever asthma the attack can be controlled by prophylactic and specific treatment. It is essential that the degree of sensitiveness be determined before administering the treatment. This may be done by testing the patient with varying dilutions of the pollen extract. He considers that it is better to give the treatment throughout the year rather than a short period of treatment during the hay-fever season. Regarding drug therapy, the author speaks of the beneficial effect of epinephrin given hypodermically in dilutions of 1 to 1000 in controlling the acute attack of dyspnea. The effects generally last for from one-half to two hours. As a rule, patients gradually become accustomed to repeated doses of epinephrin, so that the amount given has to be increased from time to time, and finally often a complete tolerance to the drug is developed and no relief is obtained from its administration. Atropin given subcutaneously or intramuscularly in gradually increasing doses up to the point of tolerance will frequently give relief. KI by mouth is frequently of distinct value. The inhalation of fumes of burning stramonium leaves and potassium nitrite gives relief in acute paroxysms.

PEDIATRICS

UNDER THE CHARGE OF

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A Case of Hypersensitiveness to Cows' Milk.—PARK (*Am. Jour. Dis. Children*, January, 1920), reports a case of a child who is now three years old. At six weeks it was given a supplementary feeding of a cow's milk formula once a day. It took about one ounce, amounting to about 10 c.c. of cow's milk. It fell asleep and when aroused it vomited. It was very pale and heavy. It refused the next breast nursing, and vomited again, after which it fell into a heavy sleep. It took the next breast feeding and the next day it seemed normal. Thinking that the baby was hypersensitive to cow's milk it was given a teaspoonful of a mixture of milk diluted one-half with water. After taking this it was nursed and immediately fell asleep. It occasionally opened its eyes and yawned. The face became flushed. About five hours after taking the mixture it vomited in small amount, and ten minutes later it vomited a large amount of bile-stained fluid. It became exceedingly pale and seemed greatly prostrated. Shortly after vomiting it had two large loose stools containing mucus. It refused the next nursing, and slept heavily until the next nursing period when it nursed in a normal manner. After cutaneous test there were delayed general reactions locally, the tests were negative. It was able to take goat's milk without any difficulty. Intracutaneous tests of various proteins were done and gave slight local and delayed general reactions. There was a

marked but delayed local reaction to cow's milk. The same general effects followed the accidental administration of a condensed milk mixture. An attempt was made to desensitize the baby, and after some time and with perseverance this was accomplished. He is now able at three years to take a pint of cow's milk daily without any difficulty. At eight months of age it was necessary to wean him from the breast, and it was necessary to feed him on goat's milk, which singularly enough gave rise to no reaction. From the evidence of the case the author considers this peculiarity as having been inherent in the germ plasm.

Dextrose Tolerance in Atrophic Infants.—MARTILL, MAYER and SEINER (*Am. Jour. Dis. Children*, January, 1920) remind us that by the Woodyatt method it has been shown that the tolerance of adults was from 0.8 to 0.9 grams per kilogram per hour. In this study they gave dextrose solutions intravenously to four non-atrophic infants, ranging in age from five to fifteen months. In these cases the tolerance was found to be 0.8 to 0.9 gram per kilogram of body weight per hour. Seven atrophic infants were studied. They showed emaciation, tendency to subnormal temperature, lack of turgor and grayish color of the skin. Their weights were stationary or nearly so. The stools were good. In no case was tolerance below 1.4 or 1.5 gram, per kilogram of body weight per hour. Other authors have also found that the metabolism of the atrophic infant proceeded to a higher level than that of the normal infant. McClure and Sauer have observed that atrophic infants have a higher surface temperature than normal infants and there is an increased insensible perspiration. An increased sugar tolerance seems to fit in very well with such observations. It was observed that the readings were constant in the cases in which several injections were given.

Mental Defectives in a Southern State.—ANDERSON (*Mental Hygiene*, October, 1919) gives a report of the Georgia Commission on Feeble-mindedness and the survey of the National Committee for Mental Hygiene. As a result of this survey he says that 40 per cent. of the inmates of the almshouses were feeble-minded. Feeble-minded families had been found in the State that had been supported by church and organized charities for three or four generations. A study of a typical orphanage showed that 28.7 per cent. of the children were feeble-minded. If the same percentage exists in the other orphanages in the State, there are at least 810 feeble-minded in orphanages who need special care and training in a school for the feeble-minded. At the state prison farm 17.5 per cent. of the inmates were feeble-minded. The striking fact at this institution was not so much the presence of feeble-minded men, but the great number of other forms of mental abnormality, mental disease and deterioration, epilepsy and the like. In this institution 65.8 per cent. of the inmates were classifiable in terms of deviation from normal mental health. Of the women inmates of the prison 42.8 per cent. were found to be feeble-minded. In the two typical county jails studied 34 per cent. of the inmates were feeble-minded, with a mental level of ten years or under. Of 122 immoral women examined 43.5 per cent. were found to be feeble-minded. The

present policy of treating these feeble-minded girls for venereal disease and then turning them into the community to acquire it over again is costly. Probably the greatest factor in the spread of venereal disease is the feeble-minded prostitute. Of 100 cases of juvenile delinquents studied in the juvenile courts, 17 per cent. were found to be feeble-minded, In one reformatory for boys, 15 per cent. were feeble-minded. In the State Reformatory for boys 24.1 per cent. were feeble-minded and in the State Training School for Girls 27 per cent. of the inmates were feeble-minded. These feeble-minded delinquent children later become the chronic habitues of the jails, courts and prisons. In the public schools 3.5 per cent.of the children examined were feeble-minded.

Control of Diphtheria by Cultures of the Noses and Throats of School Children.—GLOYNE (*Jour. Am. Med. Assn.*, January 10, 1920) gives the results obtained in Kansas City, of which he is Health Commissioner. He says that the swabbing of the throats of the children should be a measure adopted at the outbreak of a single case of diphtheria in a school. The quarantine of carriers is as essential as is the quarantine of those suffering from diphtheria. Two negative cultures should be required as the minimum from all children who have had a positive culture. A negative culture means something, but it does not have the significance that a positive culture has. Antitoxin has a very definite place in giving immunity against diphtheria, but it does not kill the diphtheria bacillus. For this reason those who have had diphtheria may continue to be carriers for an indefinite time if great care is not taken to get at least two negative cultures. Carriers usually clear up in time without the use of antitoxin.

Methods of Administering Saline and Other Solutions to Infants and Children.—AIKMAN (*Jour. Am. Med. Assn.*, January 24, 1920) says that the administering of physiologic sodium chlorid and other solutions to replace fluids lost from the body is a valuable method of carrying certain cases over critical periods. Loss of fluid is often a more serious condition in children because of the vomiting that so often accompanies grave illness, and because of the difficulty of giving water by mouth. A relative acidosis may easily result, which in a few hours may greatly increase the gravity of the attack. The reduction of fluid is more marked in cases with a history of numerous watery stools characterized by a rapid loss of weight, hollow eyes, and drawn, pinched expression of the facies. The method of greatest service is that which will permit the introduction and retention of large amounts of fluid with the greatest ease to the operator and with the least discomfort and danger to the patient. The methods used are: Administration by mouth; rectal administration; hypodermoclysis; intravenous injection by the intrasinus method or by injection into the femoral vein; intraperitoneal injection. The author has done considerable work with this method and describes it in detail as follows: The instruments needed are a medium-sized intravenous needle, an infusion bottle and rubber tubing. The skin of the abdomen is carefully sterilized with tincture of iodin and alcohol. The skin and the subcutaneous tissue are picked up between the thumb and the forefinger, and the needle is introduced in an upward direction through the abdominal wall in the midline just below the umbilicus. Care must be taken to avoid piercing

a distended bladder, and while there is also danger of puncturing the intestine, no record of this accident has been encountered. In cases in which necropsy was performed there was found a small hemorrhagic area in the abdominal wall and peritoneum, but no injury of serious importance. When the needle has passed into the abdominal cavity, the solution is introduced by gravity. It was found much easier to use the infusion bottle. Warm physiologic sodium chlorid solution has always been used, of which from 100 to 250 c.c. may be given every twelve to twenty-four hours. In older children 300 to 400 c.c. may be given and if no untoward signs develop it may be given until the abdomen is slightly distended. The injection must always be made slowly. After the operation the abdomen should be covered with a sterile dressing. It has been shown by the phenolsulphonephthalein test and by necropsy that from 40 to 60 per cent. of the fluid is absorbed in one hour. The remaining solution acts as a reserve, the gradual absorption of which explains the more protracted improvement in this method as compared to the results obtained by other methods.

Vomiting in Infants.—MARFAN (*Le Nourrison*, March, 1919) describes the vomiting of nursing children as a disease of habitual vomiting in nursing. The gastric mucous membrane is unduly sensitive and after each feeding there is a gastrospasm and the stomach casts up more or less of its contents. It is a gastric neurosis and this explains the variability of the findings in the chemistry of the stomach and of the stools. If the spasms include the bowel there is constipation. In some cases there is excessive swallowing of air. These children all show some neuropathic tendency. As regards the treatment, in some cases the treatment for inherited syphilis gives surprisingly good results. Sometimes a complete change of environment is necessary. The matter vomited in these conditions is usually a colorless fluid made up of whey, swallowed saliva and gastric juice, with floating clots of milk, as the vomiting does not occur immediately after taking food, but from fifteen minutes to one and a half hours after feeding. The vomiting may occur without effort or the child may be restless and scream and appear relieved after vomiting. Sometimes abruptly moving the child will bring on the vomiting.

GYNECOLOGY

UNDER THE CHARGE OF

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Conservative Myoma Operations.—The question of the advisability of performing myomectomy rather than hysterectomy in certain cases

of uterine myomata has been discussed on numerous occasions but as yet there is anything but unanimity on this point among gynecologists. The question has recently been investigated in the Frauenklinik at Lund by ESSEN-MOELLER (*Monats. f. Geb. u. Gyn.*, 1919, l, 36) from five different standpoints, namely the immediate operative results, ultimate results, recurrences, subsequent labors and malignant degeneration of the myomata or of the remaining uterus. Concerning the first question, in spite of the fact that for many years myomectomy has always been considered to have a higher mortality than hysterectomy, the author quotes statistics from European as well as American sources to show that such is not the case, while he personally has performed 34 myomectomies without a death. He is therefore of the opinion that the conservative myomectomy offers practically as good a primary result as hysterectomy and therefore the latter operation should be confined to those cases which are technically very difficult or in which there is malignant degeneration of the growth. Taking up the question of the ultimate results of operations he states that 80 per cent. of the cases that have had hysterectomies performed for myomata have been relieved of their symptoms while only 40 per cent. of the myomectomy cases have been so relieved since many of these latter cases continue to suffer from bleeding and annoying discharges. Therefore from this standpoint hysterectomy would be the preferable operation. Concerning the question of recurrence of myomata after the conservative operation, much will depend on the number of years elapsing between the operation and the examination, because the greater the lapse of time, the larger will be the number of cases in which a recurrence will be found. The mere fact that another myoma has grown, however, is not an indication for a second operation as many myomata give no symptoms or other inconvenience. Of the 21 patients that this author examined after myomectomy there was a recurrence in 7 but of these a second operation was necessary in only four patients. Nevertheless there can be no question but that myomectomy is distinctly inferior to the radical operation from the standpoint of recurrence. When we consider the possibility of a subsequent pregnancy after operation, there is no comparison between the two operations. Indeed it is this one point that stands as the chief argument in favor of the conservative operation since pregnancy is impossible after hysterectomy. The number of pregnancies that occur after myomectomy is doubtful, the reports of various operators giving statistics varying from 72 per cent. to 3 per cent. A close study of the literature seems to show that the possibility of subsequent pregnancy is most likely when the patient is under forty years of age and also when the tumor that was removed was of a moderate size. Large or multiple growths reduce the possibility of later gestation. In regard to the possibility of subsequent degeneration of the uterus that is left behind, the author has little to say since the pathologists themselves cannot always agree as to whether or not a given picture is malignant. The gynecologist must perform the radical operation in all cases in which there is a suspicion of malignant degeneration, which cases are usually patients over forty years of age in whom myomectomy is not the operation of choice from any standpoint.

Radium Treatment of Cervical Cancer.—KELLY and NEILL (*Am. Jour. Surg.*, 1920, xxxiii, 289) give a brief historical sketch of the use of radium in the treatment of cancer, stating that when radium was first used, and it was found that big cancers of the cervix melted down so remarkably under direct applications at the vaginal vault, a number of surgeons soon ran out before the world, waving their arms frantically like Archimedes of old and shouting, "Eureka! No more surgery; radium cures all these cases; the panacea for cancer is found at last." But the sad experience of many recurring cases began in a couple of years' time to dampen even the ardor of these neophytes, until at last a soberer judgment reigns. The present status of the case seems to be this: In early and very favorable operative cases, operation, preceded by thorough radiation, offers the best chance. Yet even here Kelly concedes that if the patient is near enough to the radium therapist to be seen at intervals, and will conscientiously keep under observation, radium alone will probably do more than operation and without risk of mutilation. He ventures to predict that within five years we are all of us likely to be using radium to the utter exclusion of operations. In all other cases, except this group, most favorable for surgery, that is to say, in all in which there is any lateral fixation of infiltration of the parametria, radium will do more for the patient than operation, for here recurrences are almost invariable. In some of these cases, as in masses of disease elsewhere, lingering nodules can often best be treated by the insertion of the minute capillary sealed glass points, each containing from three to five millecuries of emanation right into the tissues by means of a specially constructed hypodermic needle. The points are buried and lie innocuous in the tissues and the emanation sinks to zero in about five days. The authors conclude that in radium therapy, as in surgical therapy, two things are of vital importance: (1) That the earlier that the case is seen the better are the chances of a permanent result; (2) that every case ought to be followed up carefully at intervals of a few weeks or months for years. They believe that the best work in the treatment of cervical cancer will be done by the man who commands both resources and can resort with equal facility either to radium or to surgery, or can employ both conjointly as seems best.

Roentgen Treatment of Benign Bleeding.—In the treatment of the various types of uterine bleeding due to a benign cause by means of the roentgen ray, MEYER (*New York Med. Jour.*, 1920, cxi, 143) states that in a single treatment of from forty to ninety minutes' duration, depending upon the size of the patient, a permanent cessation of the menstrual function and of hemorrhage can be produced. In his last series of twenty consecutive cases, in which doses based on absorption percentage administered at a single sitting were employed, the ages ranged from seventeen to forty-five years, with no failure in the series. The symptoms of the menopause are materially diminished and the period of suffering shortened by one or two applications. The contraction of larger fibroids may require three or more repetitions of

the treatment. When more than one treatment is to be given, from four to six weeks should elapse between applications, not alone to await full reaction, but to allow the skin to recover from the cumulative effect of the rays. The fibroid growths best suited to irradiation are the intramural type. The subperitoneal and particularly the pedunculated variety had best be removed surgically according to Meyer. The submucous or polypoid type of fibroids are practically contra-indications to the use of radiotherapy. When complications, and above all malignancy do not exist, the results are uniformly good. A careful examination and correct diagnosis are essential or the result may be anything but pleasant.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
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Non-Lactose Fermenting Organisms from the Feces of Influenza Patients.—Stimulated by the occurrence of intestinal manifestations of influenza in the recent pandemic SHERWOOD, DOWNS and MCNAUGHT (*Jour. Infect. Dis.*, 1920, xxvi, 16) undertook bacteriological examination of feces of cases of this particular type. Eosin-methylene blue agar plates and Russell's medium were used for growing cultures from feces and following isolation, strains were grown on the various sugar and alcohol media. Enteriditis-like organisms were isolated from a high percentage of influenza cases of above-mentioned type. By means of agglutination and absorption tests (modified Dryer technic) strains of enteriditis like organisms were apparently placed in four groups. B. typhosus was isolated from three of 32 cases studied. There seemed to be no correlation between the nature of the stools and the presence of the enteriditis-like bacilli.

Hemolytic Streptococci in the Throat in Certain Acute Infectious Diseases.—OTTERAAEN (*Jour. Infect Dis.*, 1920, xxvi, 23) reports the relative occurrence of hemolytic streptococci in the throats of 300 patients. Swabs taken from mouth, nose and throat were cultured on blood agar plates. Fermentation tests of 50 strains gave results showing that according to Holman's classification the strains fell into the pyogenes and anginosus groups. Fifty-eight of 130 diphtheria cases and 98 of 125 scarlet fever cases gave positive streptococcus cultures. Results show that the throat is the area of predilection, while the nose and mouth do not seem to harbor the organisms frequently. The great majority of these patients were children, most of whom had more or less enlarged tonsils. Virulence for animals of the organisms studied was low. Human leukocytes, in the presence of normal human serum, easily phagocyted the hemolytic streptococci which had been

cultivated on media for a time. Other hemolytic streptococci isolated from lesions in the body where they demonstrated invasive qualities were not phagocyted until grown on artificial media, which seems to show that resistance of hemolytic streptococci to opsonins may be lost rapidly in artificial cultivation. After a comparative study the author suggests the enrichment method as preferable to direct surface plate inoculations in examinations for streptococci.

Further Attempts to Reduce the Resistance of the Guinea-pig to Tuberculosis.—Attempts were made by CORPER (*Am. Rev. Tuberc.*, 1919, iii, 605) to reduce the resistance of experimental animals to the tubercle bacilli with a view of hastening the animal diagnosis of tuberculosis. The experiments also offered an interesting study on tissue resistance when injured. A variety of methods have been advocated by various authors, for the early diagnosis of tuberculosis by injecting suspected material into different regions where tissue damage had been induced. The author studied the effect of trauma, mechanically induced or resulting from chemical irritants. Glands were crushed; lampblack or powdered glass were injected; or chemical irritants as turpentine, croton oil, cantharidin, and capsicum were injected. In the region of the injury small amounts of tubercle bacilli were inoculated, using the macroscopic-anatomic tuberculosis as an index of the acceleration of the tuberculosis in the guinea-pig. It was found that gland crushing, the injection of turpentine, croton oil, cantheridin and capsicum just prior to injection of virulent tubercle bacilli had no appreciable effect upon the infection as compared with that obtained in control guinea-pigs. Lampblack simultaneously injected with tubercle bacilli had a retarding influence while powdered glass enhanced the development of the lesions.

A Strain of Connective Tissue Seven Years Old.—An interesting report of a strain of connective tissue isolated in January, 1912, and cultivated for a period of seven years is given by EBELING (*Jour. Exper. Med.*, 1919, xxx, 531). Transfers of portions of the tissue were made each forty-eight hours into a medium composed of equal volumes of chicken plasma and chick embryo extract, under the usual aseptic precautions. These transfers were incubated at 39° C. on coverslips sealed by vaseline and paraffine, to hollow glass slides. The growth of the transferred tissue was measured by means of a projection apparatus. The rate of growth was such that transplanted fragments became 13 times their original size in forty-eight hours. The rate varied, however, up to as high as 40 times the original size, under the influence of various factors. There was noted an evident increase in the rate of growth in the last five years, thought due to the addition of the embryonic juice to the medium. It was always found that decrease in rate of growth was due to deficient medium or extract, or the presence of alkali at the surface of the slides. Plates are shown.

Streptolysin Production in Carbohydrate Media.—STEVENS and KOSER (*Jour. Exper. Med.*, 1919, xxx, 539) present a study of various factors influencing the development of hemolysins in cultures of strep tococci. A review of previous work is given. Theories of acid inhibi-

tion of growth of streptococci with subsequent diminution in hemolysins, as well as the sparing of protein metabolism (through which lysin is elaborated in the bacterial body) in the presence of fermentable carbohydrates thus diminishing lysin production. By incubating cultures of streptococci in beef infusion, peptone, serum broth for ten to fourteen hours and passing through Mandler filters they were able to obtain strongly hemolytic filtrates. Acid production in carbohydrate was followed by comparison to Sorensen series. The growth of the streptococci was followed by plate counts and stained smears. The utilization of carbohydrates by the streptococci, thus producing a luxuriant growth is at the same time accompanied by a lessened lysin production through the sparing of the proteus. The acid production reaching a value of pH 5.5 in eight hours in dextrose media, lessened the vitality of the organisms and thereby proteolysis, and is found to be destructive to hemolysin at incubator temperature. The concentration of the acid produced causes some hemolysis and a coincident brown discoloration of the hemoglobin.

The Bacteriology of Chronic Empyema.—In the past few years the bacteriology of empyema as seen in civil and especially military practice has presented several predominating types of organisms, as principal etiological factors. GORDON (*Jour. Infect. Dis.*, 1920, xxvi, 29) presents a study of the relative occurrence of these organisms and of other bacteria in empyema. The pneumococcus and streptococcus were found to be the principal primary invaders. Secondary post-thoracotomy infection, which is the rule, introduces a number of other bacteria which vary in character and quantity, as the case develops chronicity. Cultures were made on blood, beef infusion agar, from materials obtained by aspiration of pus pockets by syringe before operation, and from a looped needle introduced through a sterile tube inserted through the drainage opening, at weekly intervals. Subsequently for three months type II pneumococcus was found in one of 25 military cases, and in the other 24 hemolytic streptococci were the primary invaders. Green streptococci, Staphylococcus albus and aureus, diphtheroids and chromogenic air bacteria were found as secondary infecting agents. However, two proteolytic bacilli, one an atypical member of the proteus group, the other an atypical member of the Friedländer group were found to be the most common secondary invaders. The cultural and biological characters of these two are given. Agglutinins in the sera of 20 of 25 patients, titred from 1 : 400 to 1 : 3200 against a representative streptococcus pyogenes (Holman's classification) isolated from the chest fluid. The absence of streptococci in culture from empyema fluids at the time the serum was obtained would indicate an active immunity against those organisms. No agglutinins could be demonstrated against various streptococcus viridans strains isolated from a number of cases. Controls of serum from normal cases were negative.

Serum Reactions in Influenza.—Following their investigation of the etiology of influenza, in the recent epidemic, GAY and HARRIS (*Jour. Infect. Dis.*, 1919, xxv, 414) present results of work on rabbit immune serum, the serum of active and recovered influenza cases, and of persons vaccinated by the injection of a presumably protective dose

of a mixed vaccine comprising 18 strains of influenza bacilli. Rabbits were immunized by six to eight injections of a mixed vaccine of ten strains of Bacillus influenzæ grown on "chocolate medium," and killed by suspension in 0.5 per cent. phenolized salt solution. After a first injection of killed organisms, living cultures were employed. Agglutination tests at 37° C. for two hours, with the serum of immunized rabbits, also Pfeiffer's phenomena of bacteriolysis, conglutination and precipitin reactions were negative. Fixation antibodies were found in high dilutions. Agglutination tests with the same serum, incubating three to six hours at 55° C. were positive. A variation in the agglutinability of different strains of Bacillus influenzæ suggests the existence of different groups of the organism. In the series of human cases, agglutination tests at 37° C., conglutination, opsonin, precipitin, and intradermic tests were negative. Fixation reactions were positive in 40 per cent. of vaccinated cases and in one of twenty-nine acute cases; normal and recovered cases were negative. Agglutination tests at 55° C. were positive in from three to six hours in 88 per cent. of acute cases, 46 per cent. of vaccinated and 38 per cent. of recovered cases. The few normal cases tested were uniformly negative.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Experiments on the Nasal Route of Infection in Poliomyelitis.—Flexner and Amoss (*Jour. Exp. Med.*, 1920, xxxi, 123) state that the experiments given in their paper, notwithstanding their seeming diversity, relate to the conditions underlying the states of susceptibility and refractoriness to infection with the virus of poliomyelitis applied to the nasal mucosa. Certain monkeys are highly refractory to inoculation *via* the nares, with the virus of poliomyelitis, apparently in virtue of a power possessed by the nasal mucous membrane to destroy or otherwise render ineffective the virus applied to it. This property of the nasal mucosa appears to be distinct from any specific protective substance active upon the virus which may occur in the blood. An effective nasal mucous membrane prevents the passage of the energetically applied virus to the brain and spinal cord. The virus of poliomyelitis energetically applied to the nasal mucosa will survive for an undetermined period of time upon an ineffective, but for a relatively brief period of time upon an effective membrane. The

protective power possessed by the nasal mucosa is not in itself adequate to prevent infection with the virus introduced upon it, since slight injury to such independent structures as the meningeal-choroid plexus complex favors the passage of the virus from the nose to the central nervous organs. The normal nasal mucosa is, therefore, an invaluable defence against infection with the virus of poliomyelitis; and the number of healthy and chronic carriers of the virus is probably determined and kept down through the protective activities of this membrane. Antiseptic chemicals applied to the nasal mucosa upon which the virus has been deposited exhibit no great protective action and are of doubtful value. Indeed, it is not impossible that to the extent to which they may affect unfavorably the destructive properties of the nasal mucosa they may be even objectionable. Infection with the virus of poliomyelitis applied to the nasal mucosa under conditions favorable to the extension to the central nervous organs and multiplication there may be blocked or prevented by the injection of poliomyelitic immune serum into the blood. While the exact manner and site of attack of the immune serum upon the virus is somewhat conjectural, when all the available data are considered it seems probable that the meeting-place of the virus and immune serum is in the subarachnoid space.

The Physical and Economic Benefits of Treatment for Hookworm Disease. — SCHAPIRO (*Jour. Am. Med. Assn.*, 1919, lxxxiii, 1507) states that although the life, labor and customs of the people living on the two estates studied do not differ from those that obtain generally throughout the country (Colombia), and although every effort was exercised to guard against error in conducting the study, the number of cases studied is probably insufficient to justify the drawing of conclusions that will apply to whole territories. Nevertheless, the figures may be taken as pointing toward, if not as establishing the following: There is a permanent increase in hemoglobin as a result of treatment for hookworm disease. On one farm in spite of a 15 per cent. reduction in unit pay the laborers earn 27 per cent. more. On another, where there has been no reduction in unit pay, they earn 14.6 per cent. more. The owners of one farm are cultivating 33 per cent. more coffee with the same number of laborers at a lower unit cost. In addition to the benefits mentioned one estate reports a marked reduction in morbidity and in infant mortality, and both estates report that the laborers spend less than formerly, or else spend nothing at all, for quack medicines and quack physicians to cure their infirmities.

The Chemotherapeutics of the Chaulmoogric Acid Series and Other Fatty Acids in Leprosy and Tuberculosis—WALKER and SWEENEY (*Jour. Infect. Dis.*, 1920, xxvi, 238) state that chaulmoogra oil contains bactericidal substances that are about one hundred times more active than phenol. The bactericidally active substances of chaulmoogra oil are the fatty acids of the chaulmoogric series, chaulmoogric and hydnocarpic acids and possibly lower is omers of this series. The bactericidal activity of the chaulmoogric acid series is specific for the acid-fast group of bacteria and inactive against all other bacteria tested. This specific bactericidal activity against acid-fast bacteria is a function of the carbon ring structure of the molecule of the

chaulmoogric acid series, which, so far as known, is found only in chaulmoogra oil and in oils of certain plants closely related to Taraktogenous kurzii. The fatty acids of cod-liver oil, the salts of which constitute Roger's sodium morrhuate, used in the specific treatment of tuberculosis, do not possess the specific bactericidal activity of the chaulmoogric acid series. These facts supply a scientific basis for the use of chaulmoogra oil and its products in leprosy. Their experiments do not support the claims of Rogers for sodium morrhuate in the specific therapy of tuberculosis. The bactericidal activity of the chaulmoogric acids against all members of the acid-fast group of bacilli, together with the clinical results obtained from their use in leprosy, furnish theoretical grounds for the application of the chaulmoograte to the therapy of tuberculosis. Experiments on animals are now in progress to determine whether or not the chaulmoogric acid series have any practical value in the chemotherapy of tuberculosis.

An Experimental Study of the Efficacy of Gauze Face Masks.—KELLOGG and MACMILLAN (*Am. Jour. Public Health*, 1920, x, 34) state that gauze masks exercise a certain amount of restraining influence on the number of bacteria-laden droplets possible of inhalation. This influence is modified by the number of layers and fineness of mesh of the gauze. When a sufficient degree of density in the mask is used to exercise a useful filtering influence, breathing is difficult and leakage takes place around the edge of the mask. This leakage around the edges of the mask and the forcible aspiration of droplet-laden air through the mask is sufficient to make the possible reduction in dosage of infection not more than 50 per cent. effective. It remains for future controlled experiments on contagious disease hospitals to determine whether the wearing of masks of such texture as to be reasonably comfortable are effective in diminishing the incidence of infection. Masks have not been demonstrated to have a degree of efficiency that would warrant their compulsory application for the checking of epidemics.

Causes of Blindness. The National Committee for the Prevention of Blindness has tabulated the statistics of schools and day classes for the blind for October, 1919. Among these, out of a total of 3847; 879, or 22.8 per cent., were caused by ophthalmia neonatorum. Some of the other causes of blindness in the above total are: Blind from accident, 304; progressive nearsightedness, 80; trachoma, 53; interstitial keratitis, 178; optic nerve atrophy, 394; congenital cataract, 411; and other congenital causes, 556.

The Eye as a Portal of Infection in Respiratory Diseases.—CORPER and ENRIGHT (*Jour. Am. Med. Assn.*, 1920, lxxiv, 521) state that the eye must be considered as one of the important portals of infection in respiratory diseases, and, although the greater part of the infectious material entering by way of the eye is subsequently swallowed and passes into the gastro-intestinal tract, a small but definite portion of it finds its way into the larynx and trachea, where it may persist even as long as a week. In its passage from the eyes the infectious material traverses a definite channel, dependent on which eye it has

entered or into which it has been introduced. Infectious material that is ingested is far less likely to enter the respiratory tract than that entering by way of the eye or nose.

Studies on Preservatives of Biological Products.—NEILL (*Hygienic Laboratory Bulletin No.* 112, U. S. Public Health Service, Washington, D. C.) studied the effects of widely employed preservatives on contaminations accidentally found in biological products. He found that certain contaminating organisms were extraordinarily resistant to the killing action of phenols and of formaldehyde, though resistance to one preservative did not necessarily correspond to resistance to another. Some organisms were not killed by the maximum concentrations that may be safely used in biological products. The necessity for scrupulous care in the preparation of the products is emphasized.

Immunization Against Typhus Fever.—While the clinical evidence of successful transmission of typhus infection to laboratory animals is not very striking, yet when it is supported by properly conducted controls, it is trustworthy. By those who have had extensive experience with experimental typhus, the appearance of fever in the rhesus monkey ten days after inoculation of virulent typhus blood, and its continuance for ten days are accepted as postulates of successful infection. Since the classic cross-immunity experiments of Anderson and Goldberger conclusively demonstrated the identity of the causal agents of Mexican typhus and Brill's disease, and consequently the identity of the two, it follows that any claim for the successful isolation of the causal agent of Typhus exanthematicus would be best established on the basis of the production of experimental typhus and cross-immunity with virulent typhus blood. McCOY and NEILL (*Public Health Rep.*, June 1, 1917), in carefully controlled experiments, report complete failure with the inoculation of living and killed (60° C.) cultures of B. typhi exanthematici (Plotz) to produce either experimental infection in the rhesus monkey, or any evidence of immunity against inoculation with virulent typhus blood. They conclude merely that they have presented evidence that a bacterial vaccine prepared from B. typhi exanthematici (Plotz) failed to protect monkeys against Mexican typhus.

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All communications should be addressed to—

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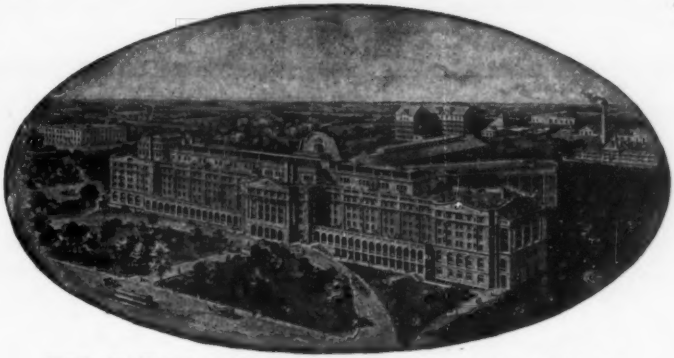

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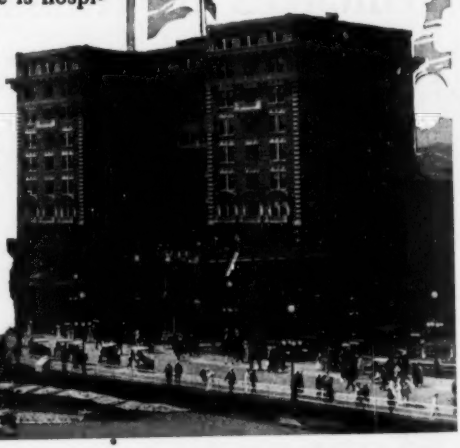

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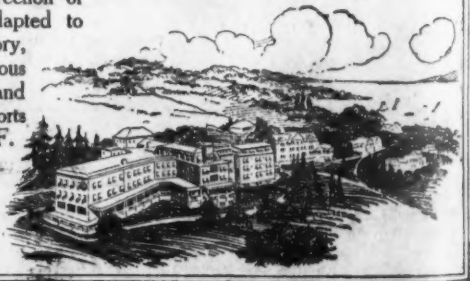

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